

Sima Jain

# Dermatology

Illustrated Study Guide  
and Comprehensive  
Board Review

 Springer

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Author and Editor

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Illustrated Study Guide and Comprehensive  
Board Review

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*To my parents, Manohar and Usha, to whom I owe so much. Thank you for teaching me the importance of hard work, for giving me strength during times of adversity and for your constant love and support. There are not enough words to express how grateful I feel to have you as my parents.*

*To my husband and best friend, Milind, for your love, patience and ability to always keep me balanced. You are my rock and constant source of inspiration, and this project would not have been completed without your unwavering support. I love you more and more each day.*



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## Preface

The idea of putting together this review book arose when I was studying for my dermatology board examination. At the time, I was unable to find a comprehensive study guide combining both high yield text and high quality images. As a result, I was forced to use multiple books for the review text and several other sources for accompanying images, which proved to be very challenging and time consuming. My goal was to create a practical review book with concise yet thorough text, while placing as many corresponding images as possible.

To allow for easy reading and referencing, the text is in a bullet format and whenever possible a table format. The high yield material is either underlined in the bulleted text or highlighted in bold in the table format. I have tried to minimize any unnecessary text in order to maximize the number and variety of images in the book. The representative photographs were carefully chosen to be high-quality, to closely parallel the representing skin disorder, and to reinforce the accompanying text. I have not included any review questions in this book as numerous study questions are already available through the Dermatology In-Review website ([dermatologyinreview.com/Galderma/](http://dermatologyinreview.com/Galderma/)).

Another unique aspect of this book is the discussion of life after the dermatology board exam. Medical training, as it exists today, does not emphasize important post-residency concepts such as understanding the elements of a physician employment contract, proper coding and documentation, and choosing between the different types of malpractice insurance. Most of us have had to learn this on our own without a specific resource to guide us, which is why I have included this information in the last chapter.

Ultimately, this book is intended as a board preparatory guide for dermatologists who are preparing for initial certification or recertification. Moreover, the topics addressed in this book are highly relevant to daily practice and may serve as an excellent reference for physicians in both dermatology and primary care. In summary, it is hoped that this will fill a real need for all dermatologists (both in training and in practice) as an essential board review book and provide an indispensable resource for all physicians.

Comments from readers for any omissions or errors would be greatly appreciated.



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## Acknowledgement

I am greatly indebted to my colleague and mentor, Paul Getz MD, for his contribution of numerous photographs used in this book. It has been a pleasure and privilege to work with him, and I want to thank him for his support, guidance and friendship.

I would like to also acknowledge the entire staff at Springer for their support, especially the editorial assistant, Joanna Perey. Words cannot express my appreciation for her incredible patience, tireless effort and dedication to this book.



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# 1

## Basic Science and Immunology

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## 1.1 EMBRYOLOGY

**Table 1-1 Development of Cutaneous Structures**

Gestational Age (Estimated)	Epidermal Development	Hair, Nail, and Gland Development	Dermal/Subcutaneous Development
<b>First trimester</b>			
~3–4 weeks	Single layer of ectoderm	Germinal layer produces entire epidermis	
~6 weeks	Outer flattened periderm and inner, cuboidal germinal (basal) layer		Germinal layer in contact w/ underlying mesenchyme
~7 weeks	Fetal <b>basement membrane</b>	Tooth primordia	
~8–12 weeks	Epidermal stratification begins ~8 week Appearance of → <b>Melanocytes</b> → <b>Langherhans cells</b> → <b>Merkel cells</b>	Completed by second trimester	Dermal-subcutaneous boundary distinct
~9–12 weeks	Appearance of anchoring filaments/hemidesmosomes	Hair follicle and nail primordia seen	
<b>Second trimester</b>			
~12 weeks	<b>Formation of dermo-epidermal junction (DEJ)</b>	<b>Nail bed starts to keratinize, proximal nail fold forms</b>	Type III collagen appears
~12–14 weeks	Parallel ectodermal ridges (fingerprints)	Eccrine and sebaceous gland primordia seen	Fibroblasts actively synthesizing collagen and elastin in dermis
~12–24 weeks	Melanin production (12–16 weeks), melanosome transfer (20 weeks)	Hair follicles differentiate during second trimester (seven concentric layers present)	
~15–20 weeks		Follicular keratinization, <b>nail plate completely covers nail bed</b>	Papillary/reticular boundary distinct, dermal ridges appear
~22 weeks		Trunk eccrine gland primordia	Elastic fiber seen
~22–24 weeks	<b>Mature epidermis complete</b> (w/ interfollicular <b>keratinization</b> )		Adipocytes appear under dermis

## 1.2 EPIDERMIS

- Functions as a mechanical and antimicrobial barrier; protects against water loss and provides immunological protection; thickness varies from 0.04 mm (eyelid skin) to 1.5 mm (palmoplantar skin)
- Divided into four layers (each with characteristic cell shape and intracellular proteins): stratum corneum, stratum granulosum, stratum spinosum, and stratum basale (germinativum); of note, stratum lucidum is additional layer in palmoplantar skin

## Keratinocytes

- **Ectodermal derivation:** keratinocytes comprise approximately 80–85% of epidermal cells
- Total epidermal turnover time: average 45–60 days (30–50 days from stratum basale to stratum corneum and approximately 14 days from stratum corneum to desquamation)
- Epidermal self-renewal maintained via stem cells in basal layer of interfollicular epithelium and the bulge region of hair follicles (latter location only activated with epidermal injury)
- Keratinocytes produce keratin filaments (syn: intermediate filaments or tonofilaments), which form the cell's cytoskeletal network; this provides resilience, structural integrity, along with serving as a marker for differentiation (i.e., basal layer: K5/14)
  - Six different types of keratin filaments: type I/II are epithelial/hair keratins, type III–VI include desmin, vimentin, neurofilaments, nuclear lamins, and nestin
  - >50 different epithelial/hair keratins, expressed as either type I (acidic) or type II (basic), and type I/II coexpressed together as a heterodimer (i.e., K5/14)
    - Type I (acidic) epithelial keratins: K9–28, chromosome 17
    - Type I (acidic) hair keratins: K31–40 (*old nomenclature: hHa1-hHa8, Ka35, Ka36*)
    - Type II (basic) epithelial keratins: K1–8 and K71–80, chromosome 12
    - Type II (basic) hair keratins: K81–86 (*old nomenclature: hHb1-hHb6*)

Of note, second cytoskeletal network formed by actin filaments

**Table 1-2 Keratin Filament Expression Pattern**

Type II	Type I	Location of Expression	Associated Diseases
1	10	Suprabasal keratinocytes	Epidermolytic hyperkeratosis (EHK), Unna-Thost palmoplantar keratoderma (PPK)
1	9	<b>Palmoplantar</b> suprabasal keratinocytes	Vorner PPK
2 (2e)	10	Granular and upper spinous layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Meesman corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	<b>Basal keratinocytes</b>	Epidermal bullosa simplex (EBS), Dowling-Degos disease
6a	16	Outer root sheath	Pachyonychia congenita I
6b	17	<b>Nail bed</b>	Pachyonychia congenita II
8	18	Simple epithelium	Cryptogenic cirrhosis
K81 K86		Hair	Monilethrix
	19	Stem cells	

Do not confuse with Dowling-Degos with Degos disease  
Dowling-Degos: AD, reticulated pigmentation over skin folds  
Degos disease (malignant atrophic papulosis): occlusion + tissue infarction

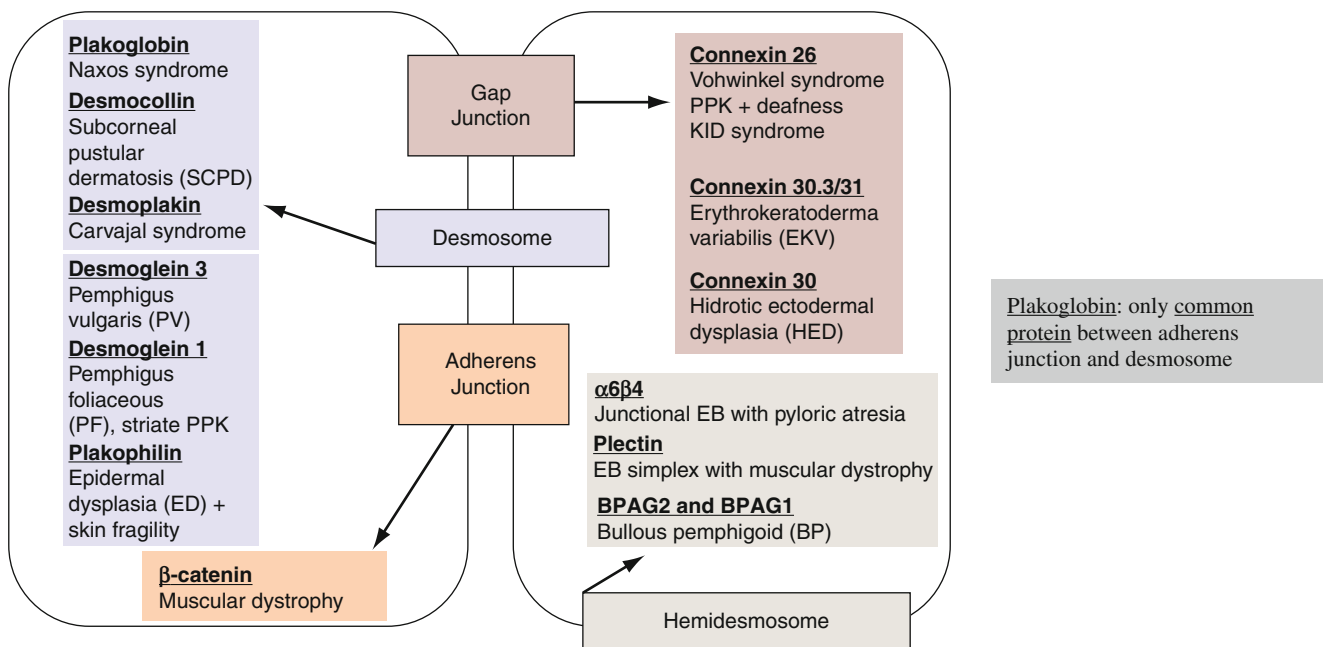
## Stratum Basale (Germinativum)

- Basal layer just above basement membrane; contains keratinocytes, melanocytes, merkel cells, and Langerhans cells (latter mainly in stratum spinosum)
- 10% of cells in basal layer are stem cells
- Expression of ornithine decarboxylase (ODC), which is a marker for proliferative activity (ODC stimulated by UVB and partially blocked by retinoic acid/corticosteroid/vitamin D<sub>3</sub>)
- De novo expression of K5/14 occurs, forming keratin filaments which insert into both desmosomes and hemidesmosomes and form keratinocyte cytoskeleton
- Hemidesmosomes allow attachment of basal keratinocyte to basement membrane

## Stratum Spinosum

- Polyhedral-shaped cells with round nucleus and ‘spiny’ appearance on H&E (due to desmosomal attachments between cells); layer contains keratinocytes and Langerhans cells
- New synthesis of K1/K10; K5/14 still present (not de novo)
- Cells contain lamellar granules (syn: lamellated bodies or odland bodies): intracellular lipid-carrying granules formed w/in Golgi in upper spinous layer; contain glycoproteins and lipid precursors which are discharged into intercellular space between granular and cornified layer; forms lamellar sheets (ceramide) or “mortar” which acts as intercellular cement for corneocytes (“bricks”), thus contributing to formation of cutaneous lipid barrier
- Types of cell junctions prominently seen in this layer and in granular layer:
  - **Desmosomes**: calcium-dependent cell-cell adhesion molecules between keratinocytes; serve as attachment sites for cytoskeleton (intermediate filaments); each desmosome made up of several proteins:
    - Transmembrane proteins: desmoglein 1/3, desmocollin 1/2 (desmosomal cadherins)
    - Desmosomal plaque proteins: plakoglobin ( $\gamma$ -catenin), desmoplakin 1/2, keratocalmin, desmoyokin, band 6 protein, envoplakin
  - **Adherens junctions** (zonula adherens): transmembrane classical cadherins (namely E and P) linked to actin cytoskeleton via cytoplasmic plaque proteins ( $\alpha$ ,  $\beta$ ,  $\gamma$ -catenin)
  - **Tight junctions** (zonula occludens): seal intercellular space, prevent diffusion of solutes between cells and maintain cell polarity; major constituents are claudins and occludins
  - **Gap junctions**: transmembrane channels formed by six connexin monomers, allows for cytoplasmic continuity and communication between cells
- Know particular diseases associated with defects or antibodies against certain cell junction proteins (Figure 1.1)

Flegel's disease, Harlequin ichthyosis: ↓ lamellar granules (LG)  
X-linked ichthyosis: absent steroid sulfatase in LG  
Congenital ichthyosiform erythroderma: ↑ LG but structurally abnormal



**Figure 1.1**  
Skin diseases associated with cell junctions

## Stratum Granulosum

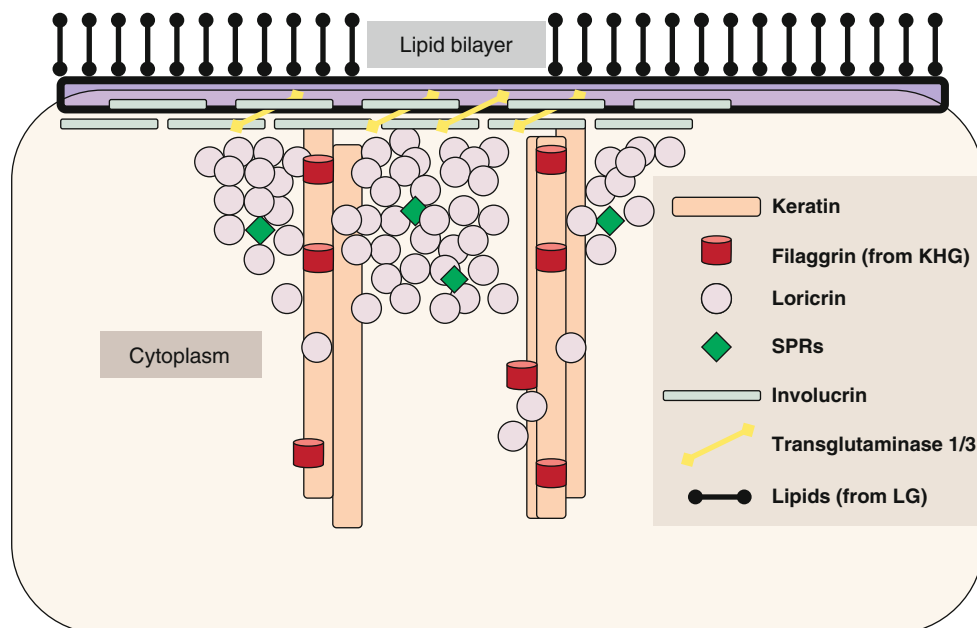
- Cells with more flattened appearance; contain dense keratohyalin granules
- Granular cells start to lose their nuclei but retain dense keratin filaments
- Expression of K2 (modified from K1) and K11 (modified from K10)
- **Keratohyalin granules (KHG)**: dense stellate globules which contain profilaggrin, loricrin, and involucrin (latter two function in cornified cell envelope)
  - **Filaggrin**: keratin filament **aggregating protein** in KHG; binds intermediate filaments and organizes into fibrils; initially cleaved from profilaggrin (when granular layer transformed into cornified layer) and is degraded into free amino acids
- **Cornified cell envelope (CE)** (Figure 1.2): highly cross-linked lipid-rich flexible structure enveloping corneocytes; serves as insoluble exoskeleton and rigid scaffold for internal keratin filaments; provides both mechanical and water permeability barrier
  - CE assembly begins in granular layer where several proteins cross-linked by transglutaminase into  $\gamma$ -glutamyl lysine isopeptide bonds  $\rightarrow$  rendering CE insoluble
  - CE comprised of lipid layer and several covalently cross-linked proteins: involucrin, loricrin, filaggrin, small proline-rich proteins (SPRs), envoplakin, and serine proteinase inhibitor called skin-derived anti-leukoproteinase (SKALP)
    - **Loricrin**: major protein component of CE, appears in granular layer within KHG along with profilaggrin, cross-links with involucrin
    - **Involucrin**: substrate for transglutaminase cross-linking in granular layer; forms insoluble cell boundary; early differentiation marker; upregulated in psoriasis

Ichthyosis vulgaris:  $\downarrow$  profilaggrin,  $\downarrow$  KHG  
Lamellar ichthyosis:  $\uparrow$  profilaggrin,  $\uparrow$  granular cell layer  
Psoriasis:  $\uparrow$  involucrin,  $\downarrow$  loricrin,  $\uparrow$  K6/16

## Stratum Corneum

- Provides mechanical protection, impermeability, and barrier to water loss
- Brick and mortar model: lipid-depleted, protein-rich corneocytes (“bricks”) surrounded by extracellular lipid-rich matrix (“mortar”)
- Corneocytes composed of high weight keratins embedded in filaggrin-rich matrix
- **Urocanic acid (UCA)**: filaggrin degradation product found naturally in the cornified layer; absorbs/blocks UV radiation and forms natural moisturization factor (NMF) with other filaggrin degradation products (amino acids, pyrrolidone carboxylic acid); NMF allows stratum corneum to remain hydrated even in drying conditions
- Ceramide is a major lipid barrier of skin; other barrier lipids include cholesterol, cholesterol sulfate, and fatty acids

Of note, steroid sulfatase cleaves cholesterol sulfate to cholesterol; enzyme abnormal in X-linked ichthyosis, resulting in more cohesive corneocytes



**Figure 1.2**  
Cornified envelope (CE)

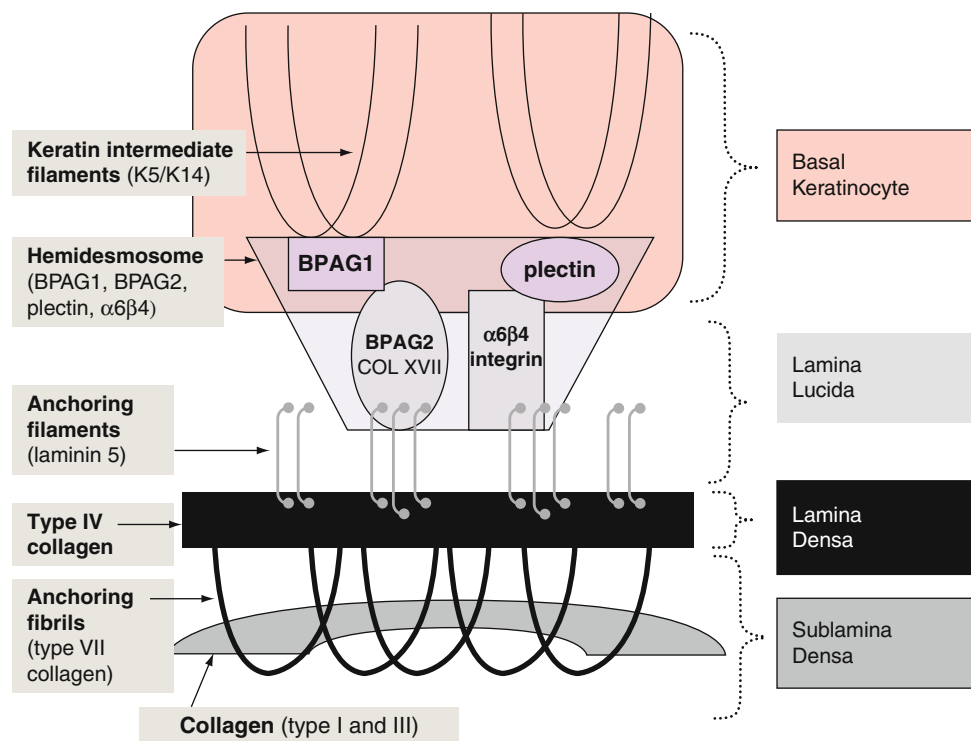
### 1.3 BASEMENT MEMBRANE ZONE (BMZ)

- Selective barrier between the epidermis and dermis; allows for interaction between the two areas and provides anchoring of epidermis to dermis
- Skin has two main BMZs: dermo-epidermal junction (major BMZ) (Figure 1.3) and dermal blood vessels
- BMZ of DEJ contains four distinct zones on electron microscopy (EM): inferior portion of basal keratinocyte, lamina lucida, lamina densa, and sublamina densa

Be able to identify BMZ components on electron microscopy (EM)

**Table 1-3 Macromolecules in BMZ**

Layer of BMZ	Structure	Associated Macromolecules
Basal keratinocyte/ Plasma membrane	Hemidesmosome	BPAG1 (230 kDa), BPAG2 (180 kDa), $\alpha 6\beta 4$ integrin, plectin
Lamina lucida	Anchoring filaments	Laminin, portion of BPAG2
Lamina densa	Anchoring plaque	Type IV collagen, laminins, heparan sulfate
Sublamina densa	Anchoring fibril	Type VII collagen, fibrillin, anchoring plaque (type IV collagen), type I and III collagen



**Figure 1.3**  
Dermo-epidermal junction zone (DEJ)

## A. INFERIOR PORTION OF BASAL KERATINOCYTE

### **Hemidesmosome (HD)**

- Appears as thickened area interspersed along plasma membrane of basal keratinocyte; provides attachment between basal keratinocyte and extracellular matrix
- Composed of following macromolecules: BPAG1, BPAG2, integrin, and plectin
- Tonofilaments (or keratin filaments) insert into hemidesmosomes

### **BPAG1 (230 kDa)**

- Intracellular glycoprotein in plakin family which is associated with the cytoplasmic plaque domain of hemidesmosome; promotes adhesion of intermediate filaments with plasma membrane (likely binds or anchors filaments to HD)

### **BPAG2 (180 kDa, Collagen XVII)**

- Transmembrane (mainly extracellular) protein belonging to collagen family; interacts with BPAG1,  $\beta 4$  integrin, and plectin
- Divisions of protein: amino terminus (intracellular), transmembrane portion, extracellular carboxy terminus (in lamina lucida); most antibodies in bullous disorders target extracellular domain (proximal NC16A and distal carboxy terminus)
  - NC16A domain (first extracellular segment): typically targeted in bullous pemphigoid (BP), pemphigoid gestationis, linear IgA bullous dermatosis (LABD)
  - Carboxy terminus (C-terminal): targeted in cicatricial pemphigoid (CP)

Three target antigens seen in CP: BPAG2, laminin-5 (epiligrin),  $\alpha 6 \beta 4$  integrin

### **Integrin**

- Transmembrane cell receptor consisting of two subunits ( $\alpha$  and  $\beta$ ); located at basal layer of epidermis and promotes both cell-cell and cell-matrix interactions
- $\alpha 6 \beta 4$ : hemidesmosome-associated integrin; binds intermediate filaments intracellularly, laminin-5 (now called laminin-332) in lamina lucida, and HD proteins (plectin, BPAG2)

Autoantibody to  $\beta 4 \rightarrow$  CP (ocular);  $\beta 4$  mutation  $\rightarrow$  JEB with pyloric atresia

### **Plectin**

- Intracellular protein belonging to plakin family; associated with cytoplasmic plaque domain of hemidesmosome; links intermediate filaments to plasma membrane and cross-links HD proteins

Plectin mutation  $\rightarrow$  EBS w/ muscular dystrophy

## B. LAMINA LUCIDA

- Electron-lucent zone under hemidesmosome on EM; weakest link of BMZ
- Comprised of anchoring filaments (laminin-332), laminin-1, fibronectin, nidogen (entactin), uncein, and portion of BPAG2

### **Anchoring Filaments**

- Delicate filaments emanating perpendicularly from HD which stretch from plasma membrane to lamina densa; product of basal keratinocytes; smaller than anchoring fibrils
- Laminin-332: also known epiligrin (truncated laminin), laminin-5, kalinin, and nicein; glycoprotein serving as major component of anchoring filaments; major attachment factor for keratinocytes and binds  $\alpha 6 \beta 4$  integrin at hemidesmosome

## C. LAMINA DENSA

- Electron-dense zone below lamina lucida appearing as dense line with closely stippled dots on EM
- Type IV collagen: major component and characteristic collagen of BMZ; highly cross-linked sheetlike pattern provides flexibility to basement membrane
- Additional components: laminins, entactin (nidogen-1), and heparan sulfate (negatively-charged hydrophilic proteoglycan which provides selective permeability barrier)

## D. SUBLAMINA DENSA

- Contains anchoring fibrils, anchoring plaques, elastic microfibrils (without elastin), and linkin

### Anchoring Fibril

- Primary constituent is type VII collagen; appears larger than anchoring filaments and emanates perpendicularly down from lamina densa into papillary dermis
- Connects lamina densa to anchoring plaques (type IV collagen) in dermal matrix
- Intercalation with banded collagen fibrils of papillary dermis: forms fan-shaped clumps

Type VII collagen autoantibodies in both EB acquisita (EBA) and bullous SLE; type VII mutation in dystrophic EB (DEB)

### Anchoring Plaque

- Primary component is type IV collagen; site where anchoring fibrils attach from above and fibrillar collagen (type I and III) attach from below; electron-dense oval structures seen under lamina densa on EM

**Table 1-4 Diseases Associated with Epidermal/Dermal Proteins**

Protein	Associated Disease
Plectin	EBS with muscular dystrophy, paraneoplastic pemphigus (PNP)
$\alpha 6\beta 4$ integrin	JEB with pyloric atresia, cicatricial pemphigoid (CP) - ocular
BPAG1	Bullous pemphigoid (BP), PNP
BPAG2	NC16A $\rightarrow$ BP, linear IgA bullous dermatosis (LABD), pemphigoid gestationis Carboxy terminus $\rightarrow$ CP
Laminin-332 (5)	JEB (Herlitz), CP ( $\uparrow$ risk of cancer)
Type VII collagen	Dystrophic EB (mutated), EBA, bullous SLE
Plakoglobin	Naxos disease
Desmocollin 1	Subcorneal pustular dermatosis (type of IgA pemphigus)
Desmoglein 1	Striate PPK, pemphigus foliaceus, pemphigus vulgaris (mucocutaneous), bullous impetigo, staphylococcal scalded skin syndrome (SSSS), PNP
Desmoglein 3	Pemphigus vulgaris (mucosal-dominant and mucocutaneous), PNP
Desmoglein 4	Monilethrix (autosomal recessive)
Desmoplakin 1/2	Carvajal syndrome, striate PPK, skin fragility/woolly hair syndrome, PNP
Plakophilin	Ectodermal dysplasia/skin fragility syndrome
Connexin 26	KID syndrome, Vohwinkel syndrome, PPK with deafness
Connexin 30	Hidrotic ectodermal dysplasia (HED)
Connexin 30.3/31	Erythrokeratoderma variabilis (EKV)
$\beta$ -catenin	Pilomatricoma (multiple may be associated with myotonic dystrophy)
Loricrin	Vohwinkel (variant), progressive symmetric erythrokeratoderma
Filaggrin/KHG	Atopic dermatitis, ichthyosis vulgaris
Transglutaminase	TG3 $\rightarrow$ dermatitis herpetiformis, TG1 $\rightarrow$ lamellar ichthyosis

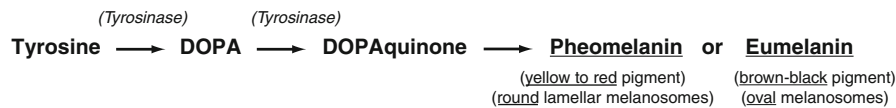
## 1.4 MELANOCYTES, LANGHERHANS, AND MERKEL CELLS

### Melanocyte

- Pigment-producing dendritic cell derived from neural crest; found in skin, hair, uveal tract of eye (choroid, iris, ciliary body), leptomeninges, and inner ear (striae vascularis of cochlea)
- Survival/migration during embryogenesis depends on specific interactions such as c-kit activation contributing to migration and development of melanocytes and melanoblasts
- Resides in basal layer with ratio of one melanocyte to ten basal keratinocytes (do not confuse with epidermal melanin unit where one melanocyte in contact with 36 keratinocytes)



- Melanocytes do not form junctions with keratinocytes (hence, artifactual halo on H&E)
- Function: production of melanin pigment with subsequent transfer to keratinocytes, absorption of UV radiation, and protection from UV-induced mutations
- Melanin: synthesized in melanosome (specialized type of lysosome) and passes through series of stages (I–IV) before melanosome transferred to keratinocyte via phagocytosis of melanocyte tips (apocytosis); melanin precursors acted upon by copper-dependent enzyme tyrosinase; two types of pigment (Figure 1.4)
  - **Pheomelanin:** red–yellow in color, synthesized in pheomelanosomes (spherical structure, microvesicular internal structure)
  - **Eumelanin:** brown or black in color, eumelanosome (oval-shaped, longitudinally oriented with lamellar internal structure)



**Figure 1.4**  
Melanin biosynthetic pathway

- Melanin stimulated by melanocyte-stimulating hormone (MSH), which is derived from larger precursor proopiomelanocortin (POMC); POMC also a precursor for ACTH, which is why ↑ hyperpigmentation seen in Addison's disease
- Melanocortin-1 receptor (MC1R) controls which type of melanin is produced by melanocytes; loss of function in MC1R results in ↑ pheomelanin (red hair) and ↓ eumelanin; thus, fair skin without the more protective pigment and more prone to damage from UV radiation with subsequent ↑ risk for melanoma
- Hair melanocytes: one melanocyte to five keratinocytes; graying caused by gradual decrease in number of follicular melanocytes
- Chronic sun exposure results in melanocytes creating larger melanosomes
- Racial differences NOT due to differences in number of melanocytes, but rather the size, distribution, and number of melanosomes (all races have SAME melanocyte density)
  - Dark-skinned: larger melanosomes, ↑ melanization, ↓ melanosome degradation, and melanosomes transferred as individual organelles
  - Light-skinned: smaller melanosomes and transferred as membrane-bound clusters (with 3–6 melanosomes)

### Langerhans Cell (LC)

Be able to identify EM image of Langerhans cell

- Bone marrow-derived dendritic cell with monocyte-macrophage lineage found in stratum spinosum; constitutes 3–5% of cells of epidermis; contains actin and vimentin
- Critical in recognizing and presenting foreign antigens to specific T lymphocytes
- Connected to keratinocytes via E-cadherin receptors
- On EM, Langerhans cell with folded nucleus and distinct intracytoplasmic organelles (Birbeck granules: rod-shaped or tennis racket-shaped with striated appearance)
- Exposure to UV radiation causes depletion of LC and decreases ability to present antigen

#### Langerhans cell histiocytosis:

Letterer-Siwe – acute disseminated

Eosinophilic granuloma – bone (cranium)

Hand-Schuller-Christian – diabetes insipidus, exophthalmos, bone lesions

Hashimoto-Pritzker – self-healing

### Merkel Cell

- Ectoderm-derived cell (less likely neural crest-derived) functioning as mechanoreceptor (slow adapting, type I); found among basal keratinocytes and positive for S100 immunostain
- Found in areas with high tactile sensitivity (lips, fingers, ORS of hair follicle, oral mucosa)

- EM shows microvilli at cell surface with dense core granules, lobulated nucleus, and intermediate filaments assuming whorled arrangement near nucleus (dot-like pattern)
- Markers: cytokeratin (CK) 20 (specific for merkel cells in skin), also contain CK8, 18, and 19
- Contain battery of neuropeptides and neurotransmitter-like substances:
  - Neuron-specific enolase (NSE), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), chromogranin A, synaptophysin, and met-enkephalin

Know neuropeptides found within merkel cells

## 1.5 DERMIS

- Mesoderm-derived components
- Divided into superficial papillary dermis and deep reticular dermis (latter with larger collagen bundles and mature branching elastic fibers)

### Collagen

- Family of fibrous proteins, 20+ genetically distinct types identified; provides structural stability and accounts for 70–80% dry weight of dermis; major dermal constituent
- Composed of three chains combined into a triple helix configuration; contains Gly-x-y repeats (glycine always third residue, x frequently proline, y often hydroxylysine or hydroxyproline)
- Collagen degraded by interstitial collagenases (metalloproteinases or MMPs)
- Collagen synthesis stimulated by retinoic acid
- Collagen synthesis inhibited by: IL-1 (↑ MMP expression), glucocorticoids, IFN $\gamma$ , TNF $\alpha$ , D-penicillamine, UV irradiation

**Glycine** is most abundant amino acid in collagen

**Table 1-5 Types of Collagen**

Collagen	Location	Associated Diseases
I	Dermis, bone, ligament/tendon	Ehlers-Danlos syndrome, arthrochalasia (EDS type VII), osteogenesis imperfecta
II	Vitreous humor, cartilage	
III	Fetal skin, blood vessels	EDS vascular (type IV)
IV	Basement membrane	Alport and Goodpasture syndrome
V	Ubiquitous	EDS classic (type I/II)
VI	Aorta, placenta	Congenital muscular dystrophy
VII	Anchoring fibrils (BMZ)	Dystrophic EB (DEB)
VIII	Cornea (Descemet's membrane)	Corneal dystrophy
IX–XII	Cartilage	–
XV–XVI	Placenta	–
XVII (BPAG2)	Hemidesmosome	Junctional EB (JEB)

Descemet's membrane: basement membrane between corneal proper substance and endothelial layer

Marfan's → **fibrillin 1** mutation; congenital contractural arachnodactyly → **fibrillin 2**  
Buschke-Ollendorf → ↑ **desmosine**; anetoderma → ↓ **desmosine**

### Elastic Tissue

- 4% dry weight; provides elasticity to skin (able to return to normal shape after deformation)
- Continuous network spanning from lamina densa of DEJ throughout dermis
  - **Oxytalan fibers**: thin fibers running perpendicular to skin surface in papillary dermis
  - **Eulanin fibers**: thicker fibers parallel to skin surface in reticular dermis
- Elastic tissue is an aggregate of two components: core of elastin (amorphous protein) surrounded by protein filaments (fibrillin)
- Desmosine and isodesmosine unique to elastic fibers; lysyl oxidase (copper-dependent enzyme) necessary for formation of elastic-specific amino acids and cross-linking
- Elastic fibers damaged by UV radiation; dermal elastosis hallmark of photodamage

## Ground Substance

- Amorphous gel-like material in which connective tissue fibers are embedded
- Primarily composed of proteoglycans: core protein complexed with glycosaminoglycan (GAG such as hyaluronic acid, dermatan sulfate, heparan sulfate, chondroitin sulfate)
- Function includes water absorption (may absorb up to 1,000 times its volume), shock-absorbing properties, and lubrication between collagen and elastic fibers
  - Aging results in ↑ dermatan sulfate and ↓ chondroitin sulfate
- Pathological accumulation seen in acid mucopolysaccharidoses due to deficiency of lysosomal hydrolases that normally cleave GAGs

## Glomus Cells

- Modified smooth muscle cells found in dermis; allows shunting of blood from arterioles to venules without going through capillaries; glomus body consists of afferent arteriole, Sucquet-Hoyer canal, efferent arteriole, and nerve fibers

## 1.6 APPENDAGEAL GLANDS AND NERVES

### A. GLANDS

#### Eccrine Glands

Presence of eosinophilic cuticle helps distinguish eccrine duct from coil histologically

- Most important function is to regulate body temperature through evaporative heat loss
- Composed of three sections:
  - **Acrosyringium**: intraepidermal spiral duct opening to surface of skin
  - **Straight duct**: within dermis and consisting of double layer cuboidal epithelium lined by eosinophilic cuticle on luminal side
  - **Secretory eccrine coil**: within deep dermis/subcutaneous fat and consists of two different cells (glycogen-rich, pale cells, and smaller darker cells) which appear to fit together in one layer, outer portion contains myoepithelial cells
- Positive for S100, keratin, and carcinoembryonic antigen (CEA)
- Found everywhere except: clitoris, glans penis, labia minora, external auditory canal, and lips
- Eccrine glands possess cholinergic innervation (acetylcholine) but paradoxically derived from sympathetic outflow (which typically uses norepinephrine, not acetylcholine), thus functionally cholinergic but anatomically sympathetic; merocrine secretion

#### Apocrine Glands

- Generally confined to axillae, breast (mammary gland), anogenital region, external auditory canal (ceruminous gland), and eyelids (Moll's gland)
- Secretion via decapitation (portion of cell pinched off and enters lumen)
- Responds mainly to sympathetic adrenergic stimuli

#### Sebaceous Glands

- Formed initially as outgrowth from upper portion of hair follicle; contains lobules of pale-staining cells characterized by lipid vacuoles; holocrine secretion with distention of sebocytes (filled with lipid vacuoles) until shed into lumen
- Found throughout skin except palms and soles
- Always associated with follicles except following locations ('free' sebaceous glands):
  - **Gland of Zeis** → found on superficial eyelid margin (near Moll's gland)
  - **Meibomian gland** → tarsal plate of eyelids (behind Moll's gland)
  - **Montgomery tubercle** → nipple and areola
  - **Tyson's gland** → external fold of prepuce (genitalia)
  - **Fordyce spot** → vermilion border of the lips and buccal mucosa
- Gland under adrenergic hormonal control; enlargement at puberty due to ↑ androgens
- Lipid composition of sebum: 57% triglycerides, 25% wax esters, 15% squalene, <3% cholesterol and cholesterol esters

## B. NERVES

- Sensory receptors divided into corpuscular (which contains non-nervous components) and free nerve endings; positive for S100 immunostain and contains neurofilaments
- Two main types of corpuscular endings: nonencapsulated (Merkel cells) and encapsulated (Meissner's and Pacinian corpuscles)
- Pain detected by nociceptors via either A $\delta$ -type fibers (large) or C-type fiber

### Nonencapsulated Endings

- **Free nerve endings:** rapidly adapting receptors; majority consist of nonmyelinated C-type fibers and some myelinated A $\delta$ -type fibers; terminal endings within epidermis and papillary dermis; mainly detects touch, pressure, and pain
- **Merkel cells:** found in basal layer and makes close contact with sensory nerve terminal (Merkel disc), detects touch

### Encapsulated Endings

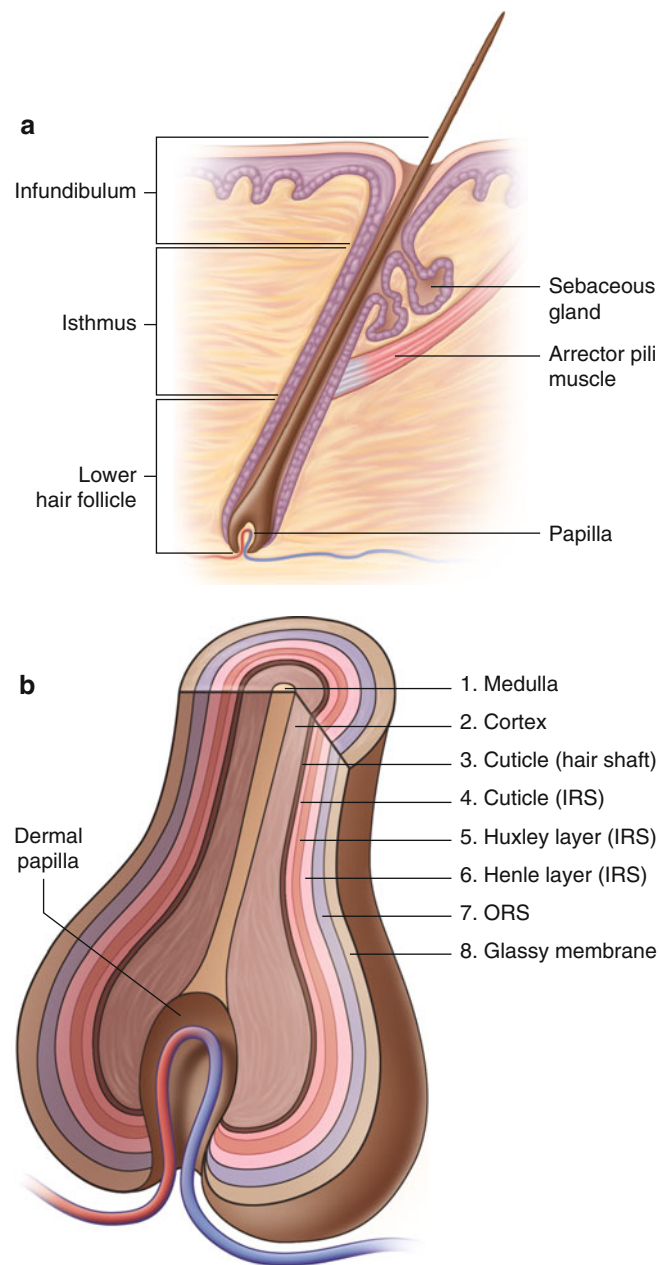
- Vater-Pacini (Pacinian) corpuscle
  - Rapidly adapting mechanoreceptor resembling an onion; found in deep dermis/subcutis
  - Detects deep pressure and vibration; increased concentration in palms/soles, nipples, and anogenital region
- Meissner's corpuscle
  - Elongated mechanoreceptor detecting light touch (resembles pine cone); located just below DEJ (dermal papillae) and highest density in palmoplantar skin
- Ruffini corpuscle
  - Thin, encapsulated, fluid-filled slow adapting receptor; found in deep dermis and detects continuous pressure
- Mucocutaneous end organs (Krause end bulbs)
  - Mucocutaneous receptors found on vermilion lip, perianal region, glans penis, clitoris, and labia minora

## 1.7 HAIR AND NAILS

### Hair

- Hair is derived from ectoderm, but dermal papilla is of mesoderm-derivation
- Hair follicle is positioned at an angle; base of follicle typically within the subcutaneous fat
- Longitudinal anatomy (Figure 1.5A):
  - **Infundibulum:** upper portion of follicle extending from surface of epidermis to opening of sebaceous gland
  - **Isthmus:** middle portion extending from opening of sebaceous gland duct to insertion of arrector pili muscle (bulge), lined by outer root sheath (ORS), no inner root sheath (IRS)
  - **Inferior segment or lower hair follicle:** extending from base of isthmus to hair bulb; consists of matrix cells and envelops dermal papilla; lined by IRS; ORS present but not keratinized; widest diameter termed critical line of Auber (below this is where bulk of mitotic activity occurs); melanocytes in bulb provide melanosomes for hair color
- Cross-sectional anatomy (Figure 1.5B) from outer to inner layer:
  - Glassy membrane → ORS → Henle's layer (IRS) → Huxley's layer (IRS) → cuticle (IRS) → hair shaft cuticle → cortex → medulla
- Important sites:
  - **ORS:** extends entire length of hair follicle; undergoes trichilemmal keratinization (no keratohyalin granules) in isthmus but changes to normal epidermal keratinization (with KHG) in infundibulum; ORS basal layer contiguous with keratinizing epidermal cells
  - **IRS:** cuticle of IRS interlocked with cuticle of hair shaft; IRS is present until bulge area, at which point it disintegrates; contains KHG in cytoplasm
  - **Cortex:** contains majority of hair keratins; **cuticle** maintains integrity of hair fibers
  - **Bulge:** thickened area of follicle wall, contains stem cells; insertion site of arrector pili
  - **Dermal papilla:** collection of mesenchymal cells which protrudes into hair bulb
- Different hair cycles (not synchronous): anagen → catagen → telogen
  - **Anagen:** hair growth phase, duration of phase determines length of hair, duration 2–6 years on scalp; 85% of hairs in this cycle at any one time

Know layers in order

**Figure 1.5****A: Longitudinal section of hair follicle, B: Cross-section of hair follicle**

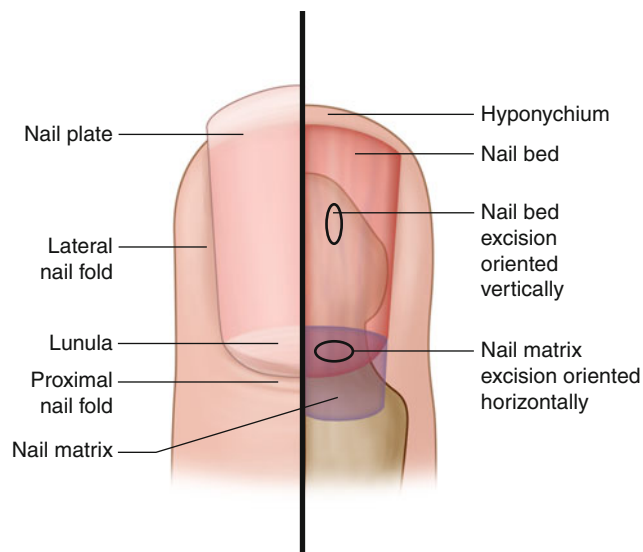
- **Catagen:** transitional phase (regression); bulb regresses and IRS lost, 2–4 week duration on scalp; 2% hairs in this cycle
- **Telogen:** resting phase, proximal hair terminal is club-shaped, duration of cycle approximately 3 months in scalp; 15% of hairs in this cycle; dermal papilla located higher up in dermis during telogen
- Growth: 0.4 mm/day, 1.2 cm/month
- Average number of hairs on scalp: 100,000 (new follicles cannot develop in adult skin); 100 hairs normally lost each day

Telogen: resting or “tired” phase

- Curly versus straight hair depends on shape of follicle (round follicle results in straight hair, oval follicle in curly hair)
- Proteins containing sulfur impart stability in keratins within the hair shaft (disulfide bonds)
- Melanocytes found in matrix area of follicle and pigment production coupled with anagen phase; no melanin formation in telogen and catagen phase

## **Nails** (Figure 1.6)

- Nail plate
  - Consists of fully cornified cells (onychocytes); created by the nail matrix epithelium
  - Proximal nail matrix synthesizes the dorsal aspect of nail plate; distal nail matrix creates the ventral surface of the nail plate
  - Pink color of nail plate due to longitudinally situated subungual capillaries
  - Nail plate has firm attachment to underlying nail bed
- Cuticle or eponychium: prevents separation of nail plate and proximal nail fold
- Nail matrix:
  - Wedge-shaped area of specialized epithelium, divided into proximal and distal portion
  - Lunula demarcates distal portion of nail matrix
  - Melanocytes found in high concentration in nail matrix (mainly seen in the distal matrix)
- Growth rate of fingernails 2–3 mm/month; toenails 1 mm/month
- Complete replacement of nail requires 6 months for fingernail and 18 months for toenail



**Figure 1.6**  
Nail anatomy

## 1.8 WOUND HEALING AND CYTOKINES

### Wound Healing

- Different overlapping events: inflammatory phase, proliferative phase, and tissue remodeling; some sources cite vascular phase (hemostasis) as first phase (Table 1-6)

**Table 1-6 Stages of Wound Healing**

<b>PHASE 1: INFLAMMATION</b> ( <i>first 6–8 h</i> ) Clot information → neutrophil/macrophages debride wound
<p>⇒ <b>Platelets (main player)</b> Release chemotactic factors (fibrinogen, fibronectin, thrombospondin, vWF, ADP) attracting other platelets, WBCs and fibroblasts; produces <b>fibronectin</b> which acts as provisional matrix for fibroblast migration; also releases PDGF, TGF<math>\alpha</math>, and TGF<math>\beta</math></p> <p>⇒ <b>Neutrophils</b> Appears first and in greater numbers than macrophages; attracted by fibrinogen, fibrin split products, leukotrienes, and C5a; important in <b>tissue debridement and bacterial killing</b></p> <p>⇒ <b>Macrophages</b> Becomes predominant leukocyte as process continues; aids in tissue debridement and <b>critical</b> for wound healing as helps transition from inflammation to repair; attracted by fibrin degradation products, fibronectin, fragments of collagen, TGF-<math>\beta</math>; release growth factors which stimulate fibroblasts and extracellular matrix (ECM) production</p>
<b>PHASE 2: GRANULATION TISSUE FORMATION</b> (5–7 days but may last longer) Keratinocyte re-epithelialization + granulation tissue formation + angiogenesis
<p>⇒ <b>Keratinocytes (main player)</b> Re-epithelialization begins several <b>hours</b> after injury; keratinocytes <b>leapfrog</b> over each other from wound edges and adnexal structures; collagenase produced and aids in migration</p> <p>⇒ <b>Fibroblasts</b> Migrates to wound 48 h after injury, move along fibronectin matrix from initial clot; type III collagen in early wound; contraction by myofibroblasts (typically second week of healing)</p> <p>⇒ <b>Blood vessels</b> Stimulation of new vessel growth via VEGF, TGF-<math>\beta</math>, thrombospondin, angiotropin, angiogenin, and SPARC (secreted protein acidic and rich in cysteine)</p>
<b>PHASE 3: TISSUE REMODELING</b> (after third week) Granulation tissue become mature scar tissue
<p>⇒ <b>Fibroblasts (main player)</b> Produces fibronectin, hyaluronic acid, collagen → key role in cell migration/tissue support; fibronectin for cell migration and template for collagen deposition</p> <p>⇒ <b>Collagen</b> Granulation tissue initially composed of type III collagen; gradually replaced by type I collagen and scar's tensile strength increases; final strength only 70–80% preinjured skin</p>

Scar strength: 5% at 1 week, 20% at 3 weeks, 70–80% at 1 year



## 1.9 IMMUNOLOGY

- Immune system divided into innate and adaptive immunity based on specificity of response and presence/lack of immunologic memory

**Table 1-7 Innate and Adaptive Immune System**

Innate Immunity	Adaptive Immunity
First line defense; rapid but less controlled	Delayed initial response but more specific
No memory	Memory
Nonspecific receptors (R) recognize nonself pathogens	Gene rearrangement specific for individual antigen (Ag)
Cannot bind to self antigens	Can bind to self and nonself antigens
Noncellular Components	
Antimicrobial peptides: <b>canthelicidins</b> and <b>defensins</b>	Antibodies
Cytokines (IL-1, IL-10, IL-12, IFN $\alpha$ , IFN $\beta$ )	Cytokines (IL-2, IL-4, IL-5, IFN $\gamma$ , TGF- $\beta$ )
Complement	Complement
Toll-like receptors (TLR) and nucleotide oligomerization domain (NOD) receptors: recognize pathogen-associated molecular pattern (PAMPs)	
Cellular Component	
Macrophages, neutrophils, NK cells, mast cells, and eosinophils	T cells, B cells, and Langerhans cells

### A. NONCELLULAR COMPONENT

#### Cytokines (Table 1-8)

- Cytokines are small proteins secreted by cells that modulate functional properties of the cytokine producing cell or other local/distant cells (autocrine, paracrine, or endocrine manner); plays crucial role in intercellular communication and affects proliferation and differentiation of cells; vast majority of cytokines produced by T cells
- Cytokines classified as interleukins, lymphokines, or chemokines based on their function and cellular source; chemokine is a specific class of cytokines with ability to stimulate leukocyte mobility (chemoattraction) and direct migration (chemotaxis)
- Keratinocytes: major source of cytokines in skin, including TNF $\alpha$ , IL-1, IL-6, IL-7, IL-8, IL-10, and IL-18

#### Toll-Like Receptors (TLR) (Table 1-9)

- Family of receptors recognizing conserved patterns in microorganisms (PAMP on surface of pathogen); each TLR has multiple leucine-rich repeats and binds multiple PAMPs
- TLRs primarily expressed in immune cells and serve as first line defense; activation of TLR signaling induces expression of proinflammatory cytokines, chemokines, and plays role in adaptive immunity (dendritic cells present pathogen-derived antigen from TLR to T cells)
- TLRs bridge innate immune system to adaptive immune system
- TLR pathway results in NF $\kappa$ B activation

NF $\kappa$ B: protein complex that controls transcription of DNA

#### Complement System (Figure 1.7)

- Small proteins found either circulating in blood or on the surface of cell membranes
- Function to destroy invading microorganisms but leave host tissue intact; occurs via opsonization (complement proteins coat pathogenic organism to enhance phagocytosis) and direct membrane damage; plays role in both innate and adaptive immune system
- Complement cascade: proteins circulate as proenzymes, which upon activation are able to cleave/activate next protein in cascade; one enzyme can cleave many substrates, resulting in massive amplification
- Other roles include chemotaxis, immune complex solubilization and removal, B cell activation, and anaphylaxis (via degranulation of neutrophils and mast cells)
- Three complement pathways: classical, alternative, and mannose-binding lectin pathway



**Table 1-8 Cytokines**

Cytokine	Produced by	Function
IL-1	Monocytes, macrophages, keratinocyte	<b>Proinflammatory</b> Corticosteroid downregulates IL-1 production Triggers host innate inflammatory response (i.e., macrophages), induces fever, ↑ production of acute phase reactant, vascular endothelial cells with ↑ expression of adhesion molecules (↑ chemotaxis)
IL-2	Activated T cells	<b>T cell stimulator</b> ↑ Growth and activation of T, NK, and B cells
IL-3	T cells	Growth of mast cells and enhanced basophil production, stimulates myeloid cells
IL-4	T <sub>H</sub> 2 cells	↑ <b>T<sub>H</sub>2 response</b> Stimulates B/T cells (T <sub>H</sub> 2), induces B cell class switching to IgE, ↑ MHC II production
IL-5	T <sub>H</sub> 2 cells, mast cells	<b>Eosinophil stimulator</b> Also stimulates B cells and Ig production (↑ IgA production)
IL-6	Mainly lymphoid cells, endothelial cells	<b>Proinflammatory</b> Produces acute phase proteins, stimulates B cells to differentiate to plasma cells and ↑ antibody secretion, ↑ neutrophil production
IL-8	Keratinocyte, endothelial cells	<b>Neutrophil chemotaxis</b> Member of CXC chemokine family
IL-10	T <sub>H</sub> 2 cells, keratinocytes	<b>Anti-inflammatory</b> Inhibits proinflammatory cytokines along with inhibition of macrophages/dendritic cells; activates B cells, downregulates T <sub>H</sub> 1 response
IL-12	Mononuclear phagocytes, dendritic cells	↑ <b>T<sub>H</sub>1 response</b> Proinflammatory cytokine, induces cell-mediated immunity (i.e., NK cells), ↑ synthesis of IFN $\gamma$ and TNF $\alpha$
IL-15	Mononuclear phagocytes	<b>Proliferative</b> ↑ NK cell proliferation, ± T cell growth factor
IL-18	Activated T cells	<b>Proinflammatory</b> IFN $\gamma$ -inducing factor
TNF $\alpha$	T cell, mononuclear phagocyte, mast cell, keratinocytes	<b>Proinflammatory</b> Releases other proinflammatory cytokines (IL-1, IL-6), ↑ MHC I/II, activates T/B cells, induces fever and catabolism (cachexia)
IFN $\alpha$	Leukocytes, fibroblasts	<b>Antiproliferative</b> Antiviral, anti-oncogenic, ↑ MHC I/II expression, activation of NK cells, antifibrotic properties, inhibits angiogenesis
IFN $\beta$		
IFN $\gamma$	T cells, NK cells	↑ <b>T<sub>H</sub>1 response</b> Primes macrophages, causes B cell switching to produce Ab, good for opsonization, ↑ MHC expression, inhibit T <sub>H</sub> 2 response
TGF- $\beta$	Activated platelets, keratinocyte	<b>Anti-inflammatory</b> Induces apoptosis, inhibits growth of many cell types, counteracts proinflammatory cytokines

Of note, aberrant TGF- $\beta$  expression is implicated in the pathogenesis of fibrosis in systemic sclerosis (SSc)

**Table 1-9 Toll-Like Receptors (TLRs)**

TLRs	Function/Association
<b>TLR1</b>	Favors T <sub>H</sub> 1 response and enhances TLR2 signaling
<b>TLR2</b>	Required for recognition of bacterial <b>lipopolysaccharide (LPS)</b> ; associated with <b>inflammatory acne</b> ; of note, anti-inflammatory effect of <b>retinoids</b> via TLR2
<b>TLR3</b>	Recognizes <b>viral dsDNA</b>
<b>TLR4</b>	Recognizes <b>LPS</b>
<b>TLR5</b>	Recognizes <b>flagellin</b> (component of bacterial flagella)
<b>TLR7</b>	Recognizes <b>viral ssRNA</b> and triggers IFN $\gamma$ production; <b>imiquimod</b> (type of imidazoquinoline) is a synthetic TLR7 analog (antiviral/antitumor properties)

**Table 1-10 Antimicrobial Peptides**

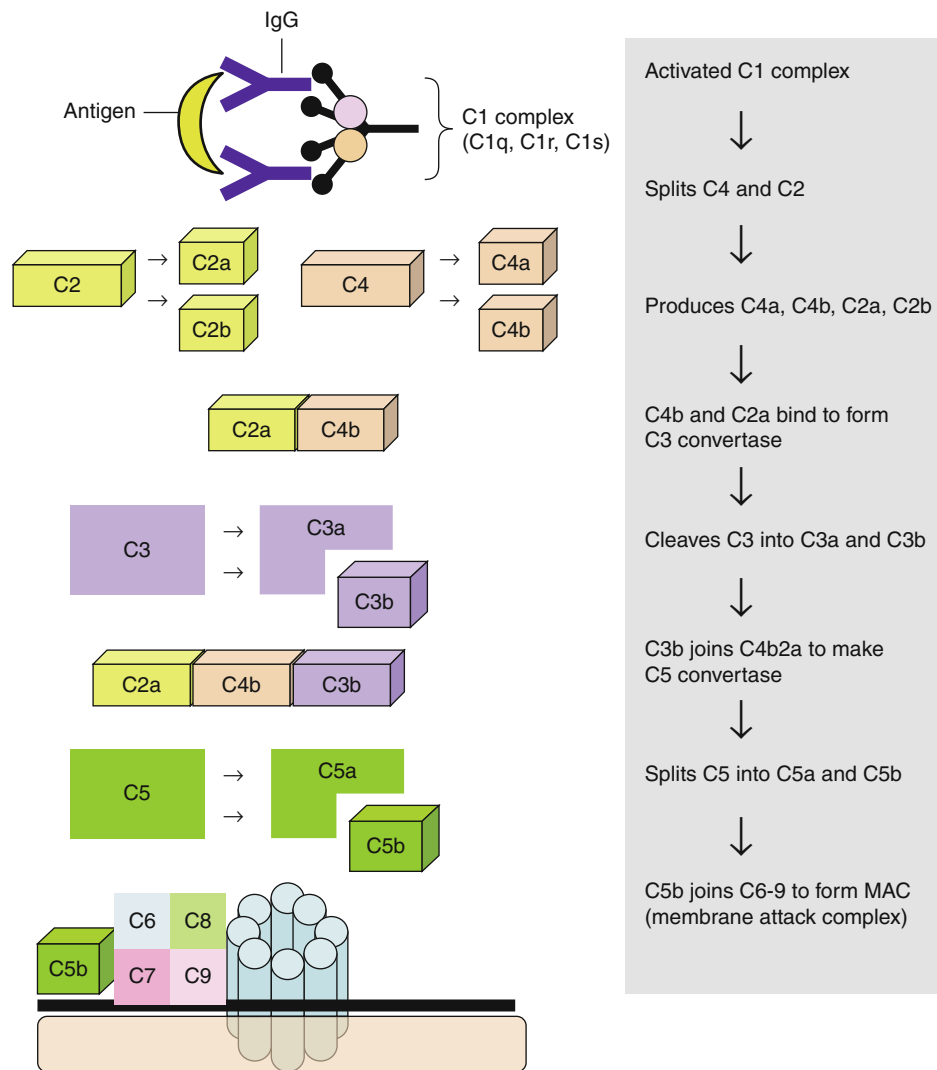
Antimicrobial Peptide	Cellular Source	Expression
<b>Human <math>\beta</math>-defensin 1 (hBD-1)</b>	Keratinocytes	<b>Constitutive expression</b> , direct chemoattractants for immature dendritic cells and memory T cells
<b>Human <math>\beta</math>-defensin 2 (hBD-2)</b>	Keratinocytes	<b>Inducible</b> with bacteria or cytokines
<b>Human <math>\beta</math>-defensin 3 (hBD-3)</b>	Keratinocytes	Inducible with bacteria or cytokines
<b>Human <math>\beta</math>-defensin 4 (hBD-4)</b>	Keratinocytes	Inducible with bacteria or cytokines
<b>Canthelicidin (LL-37)</b>	Keratinocytes, granulocytes	Inducible with bacteria or cytokines
<b>Psoriasin</b>	Keratinocytes	Inducible with bacteria or cytokines
Other peptides: <b>antileukoprotease (ALP)</b> , <b>dermicidin (DCD-1)</b> , <b>lysozyme</b>		

**hBD-2 and LL37:** ↓ levels in atopic dermatitis, ↑ levels in psoriasis

- All three pathways form membrane attack complex or MAC (C5b–C9), which is the cytolytic end-product of the complement pathway; MAC causes insertion of molecules into the lipid bilayer and forms pores (transmembrane channels), resulting in osmotic lysis of cell
- Classical pathway
  - Proteins indicated by “C” followed by number, which reflects order in which activated; when complement protein cleaved, typically results in fragmentation and lower case letter (i.e., C4**b**)
  - Activated by antigen-antibody complex with IgM or IgG (IgG3 > IgG1 > IgG2)
  - Classical proteins: C1, C2, C3, and C4
  - C1 consists of trimer with three proteins: C1q, C1r, and C1s
  - Cascade involves three main steps: activation of C3 convertase, activation of C5 convertase, and formation of MAC
  - Cascade: C1q binds to antigen-bound IgM or IgG (Ag-Ab complex) → activates C1r/C1s → C1s activates C2 and C4 (both cleaved into fragments: C2a/C2b, C4a/C4b) → C4b/C2a forms classical C3 convertase → C4b2a cleaves C3 (C3a/C3b) → C3b attaches to C3 convertase (C4b2a3b) forming classical C5 convertase → cleaves C5 → activates MAC formation → results in cell lysis
- Alternative complement pathway
  - Activated by bacterial or viral products (i.e., LPS from gram-negative bacteria) in absence of antibody
  - Alternative proteins: Factor B, Factor D, Factor H, C3 and properdin
  - C3 spontaneously cleaved at low levels (into C3a and C3b fragments) → membrane-bound C3b binds to Factor B → Factor B cleaved by Factor D into Ba and Bb → Bb stays associated with C3b forming C3bBb (C3 convertase) → properdin stabilizes C3 convertase → C5 cleaved and MAC formation occurs
- Mannose-binding lectin pathway
  - Triggered by interaction of microbial carbohydrates with mannose-binding proteins (in absence of antibody); end result is MAC formation

Be able to distinguish proteins in classical and alternative pathway

IgG4 does not cause classical pathway activation



**Figure 1.7**  
Classical complement pathway

## B. CELLS OF THE IMMUNE SYSTEM

- Responsible for specificity of immune reaction; activated by specific antigens to produce antibodies, cytokines (CD4 T cells), or direct cytotoxicity (CD8 T cells)
  - Lymphocytes:** natural killer (NK) cells, B cells, and T cells
  - Monocytes:** macrophages and dendritic (Langerhans) cells
  - Granulocytes:** neutrophils, eosinophils, and mast cells

### B Cells

- 5–10% circulating lymphocytes; arise from progenitor stem cell in bone marrow
- Express Ag-specific receptors on surface of cell; can present Ag to T cells but main function is development into plasma cells and produce Ab
- Primary immune response: naïve B cells encounter Ag → differentiate into memory cells or plasma cells; IgM produced initially but with help of T cells, B cells produce IgG, IgA, and IgE
- Secondary immune response: memory B and T helper cells re-exposed to Ag → memory B cells rapidly develop into plasma cells and release ↑↑ amount of Ab (faster, more efficient)

**Table 1-11 Complement Fragments**

Complement	Function
C3a	Neutrophil chemoattractant
C3b	Potent agent of opsonization
C3a, C4a	Weak anaphylatoxins (promote inflammatory response by binding to complement receptor on mast cells and triggering release of histamine)
C1 inhibitor	Blocks spontaneous activation of C1 by plasma proteases
C5a	Most potent anaphylatoxin (neutrophil/mast cell degranulation, increased vascular permeability, chemoattraction)
C5b	Point of assembly for MAC formation

**Table 1-12 Complement Deficiencies**

Complement	Function
↓ C1 inhibitor	Hereditary angioedema (HAE); low levels in acquired angioedema as well
↓ C1–C4 (includes C1q, C1r, C1s)	Increased risk of infections (especially encapsulated organisms like pneumococcus), SLE
↓ C3	Increased risk of infections, SLE, partial lipodystrophy, and glomerulonephritis
↓ C5–C9	Increased susceptibility to neisserial infections

- Receptors/markers: MHC II molecules, complement receptors (recognize opsonized antigens), Fc receptors (immunoglobulin constant region), CD19, CD20, and CD79a
- Isotype switching occurs in presence of specific cytokines

## T Cells

- 70–75% circulating lymphocytes
- Arise in bone marrow, mature in thymus, and divide into helper T cells (CD4) and cytotoxic T cells (CD8); recognize fragments of Ag/peptide bound to MHC molecule on cell surface and play major role in immune regulation via secretion of cytokines or direct cell lysis
- Need two signals for activation: TCR/MHC and CD28/B7 binding
- Helper T cells further subdivided into T<sub>H</sub>1 and T<sub>H</sub>2 cells
- T<sub>H</sub>1 cells
  - Mediate delayed-type contact hypersensitivity reactions, ↑ cell-mediated immunity, activate macrophages, produce IL-2, ↑ IgG production, ↓ IgE production, downregulate T<sub>H</sub>2 response via IFN $\gamma$
  - Optimal immunity against viruses and intracellular bacteria
  - T<sub>H</sub>1 cytokines: IL-2, IL-12, IFN $\gamma$  (latter main macrophage activating cytokine), and TNF $\alpha$
  - Diseases associated with T<sub>H</sub>1 cytokine profile: allergic contact dermatitis, tuberculoid leprosy, cutaneous leishmaniasis, psoriasis (latter T<sub>H</sub>17)
- T<sub>H</sub>2 cells
  - Upregulate humoral immunity by producing IL-4 and IL-5, activate eosinophils, induce switching to IgG4 and IgE, and suppress macrophage activity, downregulates T<sub>H</sub>1 response via IL-10
  - Optimal immunity against viruses, extracellular bacteria and parasites
  - T<sub>H</sub>2 pattern: IL-4, IL-5, IL-6, and IL-10
  - Diseases with T<sub>H</sub>2 profile: atopic dermatitis, lepromatous leprosy, disseminated leishmaniasis, Szary syndrome, and parasitic infections
- Cytotoxic (CD8) cells
  - Results in lysis of cells (either foreign or host cells containing foreign proteins): CD8 binds MHC I during Ag presentation → CD8 cell releases perforin, granzymes, and granulysin → apoptosis of target cell; may also undergo apoptosis via FAS/FAS ligand

**Table 1-13 Surface Molecules of T Cells**

Surface Molecule on T Cell	Function
CD2	Binds LFA3 on Ag presenting cell (APC)
CD3	Present on all T cells
CD4	Seen in helper T cells, binds MHC II
CD8	Seen in cytotoxic T cells, binds MHC I
CD28	Binds B7 on APC
LFA1 (leukocyte function antigen)	Binds ICAM1 on APC (promotes adhesion)
CCR5	Co-receptor used for HIV entry

### NK Cells

- 2% circulating lymphocytes, derived from bone marrow, lack specific TCR for Ag recognition; important component of innate immune system
- NK cells identify transformed (tumor) or virally infected cells through the downregulation of MHC I
- Destroy cells via granzymes (induce apoptosis by initiating DNA fragmentation) and perforins (forms pores in cell membrane); may also destroy via FAS and TRAIL ligands
- Activated by IL-2, IL-12, and IL-15; express CD2 (no CD3), CD56, and CD16

### Mononuclear Phagocytes

- Referred to as monocytes when in bloodstream but called macrophages when in tissue
- Identify pathogens using opsonin receptors, mannose receptors and TLRs; destroy pathogens via reactive oxygen intermediates and lysosomal enzymes
- Degrade foreign antigens or cells into peptides and present to T cells; produce cytokines
- Receptors/markers found on cell: Fc receptor for IgG, complement receptor, MHC II

### Neutrophils

- Most abundant leukocyte with major function being phagocytosis
- Destroy pathogens in similar manner to macrophages; reactive intermediates and lysosomal enzymes contained in storage granules and classified as below:
  - Azurophil granules (primary): myeloperoxidase, lysozyme, defensins, proteinase-3, cathelicidin, and cathepsin B/D
  - Specific granules (secondary): lysozyme, collagenase, alkaline phosphatase, phospholipase A, and lactoferrin
  - Small storage granules: gelatinase, plasminogen activator, and cathepsin B/D
- Two enzymes allow formation of reactive oxygen species (ROS) which are needed to efficiently kill engulfed bacteria: myeloperoxidase (MPO) and NADPH oxidase
  - **MPO**: most effective microbicidal mechanism, responsible for green color of pus
  - **NADPH oxidase**: defect results in inability to kill intracellular catalase-positive pathogens; defect seen in chronic granulomatous disease (CGD) where bacteria unable to reduce the dye nitroblue tetrazolium (NBT) during phagocytosis (unable to reduce yellow NBT dye to blue insoluble dye)
- Cells express receptors for IgG and complement

### Eosinophils

- Major function in allergic reactions and protection from parasitic infections; regulated by  $T_H2$  cytokines (IL-5); weakly phagocytic
- Harbor granules containing major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN): all released upon activation; MBP induces mast/basophil degranulation
- Major source of cytokines: chemokines (eotaxin, MIP, RANTES), lipid mediators (leukotrienes, platelet-activating factor), cytokines (IL 2–6, 8, 12, IFN $\gamma$ , TNF $\alpha$ ), cytotoxic products (MBP, EPO, EDN, ECP), and neuromediators (substance P, VIP)

## Mast Cells

- Derived from bone marrow (CD34+ cells), often in perivascular spaces
- Contain proinflammatory and vasoactive mediators; play important role in wound healing, allergy, anaphylaxis, urticaria, and angioedema (Tables 1-14, 1-15)
- Mast cell proliferation dependent on ligand for c-kit receptor (syn: steel factor, mast cell growth factor, stem cell factor); c-kit encodes a tyrosine kinase receptor and an activating mutation in c-kit proto-oncogene can be associated with childhood and adult-onset mastocytosis
- All mast cells express high affinity receptors for IgE (FcεRI) on their surface; cross-linking of receptor-bound IgE results in release of mast cell granule contents (preformed or newly formed)
- Of note, patients with chronic urticaria may have circulating antibodies to FcεRI on mast cell surface

**Table 1-14 Mast Cell Mediators**

Mediator	Function
<b>Preformed Mediators</b>	
Histamine	Vasodilatation, smooth muscle contraction, increased vasopermeability
Heparin (Proteoglycan)	Anticoagulant, anti-complement activity, regulate activity of other mediators
Tryptase	Serine protease
Chymase	Serine protease
Carboxypeptidase-A	Protease
Cathepsin G	Protease
<b>Newly-Formed Mediators</b>	
Prostaglandin D <sub>2</sub> (PGD <sub>2</sub> )	Smooth muscle contraction
Leukotrienes (LTC <sub>4</sub> , LTD <sub>4</sub> , LTE <sub>4</sub> )	Lipid mediators
Platelet-activating factor (PAF)	Vasconstriction, platelet aggregation, smooth muscle contraction, chemotaxis for eosinophils and neutrophils
<b>Cytokines</b>	
Either preformed or newly-formed: TNFα, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13	

Of note, **PGE2** has inhibitory effect on mast cell degranulation

**Table 1-15 Triggers for Mast Cell Degranulation**

Mast Cell Degranulating Stimuli
Specific antigens (which result in bridging of FcεRI)
Anti-FcεRI autoantibodies
IL-3
Stem cell factor (SCF)
C3a, C4a, C5a (anaphylatoxin)
Drugs: NSAIDs, opiates, aspirin, vancomycin, polymyxin B, curare
Radiocontrast media
Some neuropeptides (i.e., substance P)

### Langerhans Cells (LC)

- Dendritic-shaped cells derived from bone marrow; found in epidermis, lymph nodes, and spleen; excellent antigen-presenting cells but poorly phagocytic
- After antigen captured, LC migrates to regional lymph node and presents Ag to T cells (as processed peptide with MHC molecule) → subsequent T cell activation
- Adhere to keratinocytes via E-cadherin; express B7 (CD80 or 86) after activation by antigen
- Identified by cytoplasmic rod-shaped or racket-shaped organelles (**Birbeck granules**) on EM
- LC markers: **CD1a** (exclusive to LC), S100, vimentin, and **langerin** (now useful marker)

### Antibodies (Ab)

- Produced by plasma cells; known collectively as immunoglobulins (Ig) and consist of two identical heavy chains and light chains linked by disulfide bonds
- Each Ab with unique domain which recognizes and binds Ag epitope
- Ab function: neutralize microbes/toxins by direct binding, through enhanced opsonization and/or lysis (latter via complement activation)
- Different classes based on structure of heavy chain; Ig class switching regulated by cytokines derived from T cells
- Opsonizing Abs: **IgG1/IgG3**
- Neutralizing Abs: IgA1/IgA2 (mucosal), IgG2/IgG4 (tissue)
- Cleavage of immunoglobulin by papain results in two identical Fab fragments (antigen-binding fragment) and one Fc fragment (involved in complement activation and opsonization)

Fc stands for fragment that spontaneous crystallizes

**Table 1-16 Classes of Immunoglobulins**

Ig	Characteristics
IgA	Dimer, predominantly in <b>mucosal</b> surfaces, can activate complement system via <b>alternative</b> pathway (not classical pathway)
IgD	Little known function; present as surface receptor on mature B cells
IgE	Classic anaphylactoid antibody; binds allergens and releases mast cell mediators; increased in atopic patients
IgG	Most abundant Ig; four subclasses (IgG1–IgG4) which differ in ability to activate complement, IgG1/IgG3 (potent activators) > IgG2 > IgG4 (weak to none), able to <b>cross placenta</b> , abundant production with secondary response, best for <b>opsonizing/fixing</b> complement
IgM	<b>Pentamer</b> (five Ig molecules), largest in size, major Ig production in <b>primary</b> immune response, <b>most efficient</b> at activating complement cascade, not involved in opsonization, does not cross placenta

### Major Histocompatibility Complex (MHC)

- Large genomic family of membrane-bound glycoproteins that play important role in immune system and autoimmunity; main role to present protein antigen to T cells
- Three classes: MHC I (present on all nucleated cells), MHC II (present only on antigen-presenting cells or APCs), and MHC III
- MHC I:
  - Process/bind intracellular antigens
  - Antigens are taken up and degraded in cytosol of cell
  - MHC I recognized by CD8 T cells
  - Main types of MHC I genes: HLA-A, HLA-B, and HLA-C
- MHC II
  - Process/bind extracellular proteins via degradation in endocytic vesicles (of APCs)
  - MHC II recognized by CD4 T cells
  - MHC II genes: HLA-DP, DLA-DQ, and HLA-DR
- Know following diseases with HLA associations (Table 1-17)

Remember: (MHC) 1 × 8 (CD8 T cell) = (MHC) 2 × 4 (CD4 T cell)



**Table 1-17 MHC I-Associated Diseases**

HLA	Associated Diseases
HLA-B8	Oral lichen planus, dermatitis herpetiformis
HLA-B13	Guttate psoriasis, erythrodermic psoriasis
HLA-B17	Guttate psoriasis, erythrodermic psoriasis
HLA-B27	Psoriasis vulgaris, <b>psoriatic arthritis</b> , ankylosing spondylitis, <b>reactive arthritis</b> (Reiter disease), acrodermatitis continua of Hallopeau, lichen planus
HLA-B51	<b>Behcet's disease</b> , lichen planus
HLA-B57 (Bw57)	Oral lichen planus (in English patients)
HLA-Cw6	<b>Psoriasis</b> (influences early onset)

Most definitive for psoriasis

**Table 1-18 MHC II-Associated Diseases**

HLA	Associated Diseases
HLA-DR1	<b>Lichen planus</b> (oral and cutaneous)
HLA-DR2	Lupus
HLA-DR3 (DRw3)	Dermatitis herpetiformis, pemphigus gestationis, lupus erythematosus, lichen planus
HLA-DR4 (DRw4)	<b>Pemphigus vulgaris</b> , idiopathic <b>chronic urticaria</b> , pemphigoid gestationis, rheumatoid arthritis
HLA-DR6 (DRw6)	Pemphigus vulgaris
HLA-DR10	Lichen planus
HLA-DQ2 (DQw2)	<b>Dermatitis herpetiformis</b> (strongest association)
HLA-DQ8	Dermatitis herpetiformis, chronic urticaria

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## Dermatology

# 2

# Pediatric Dermatology

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## 2.1 NEONATAL DERMATOLOGY

### **Transient Neonatal Pustular Melanosis** (Figure 2.1A)

- Onset at birth; common in darkly pigmented infants
- Presents with small pustules or residual hyperpigmented macules with collarette of scale
- Smear of sterile pustule shows numerous neutrophils
- Histology: subcorneal pustules with neutrophils

### **Erythema Toxicum Neonatorum**

- Onset typically 24–48 h after birth; occurs in half of all full-term infants
- Presents with blotchy erythematous macules, papules, pustules, and wheals
- Smear of sterile vesicle/pustule shows eosinophils
- Histology: subcorneal pustules with eosinophils, associated with pilosebaceous unit

### **Neonatal Cephalic Pustulosis (Neonatal Acne)** (Figure 2.1B)

- Onset typically within first 30 days; *Malassezia* spp. implicated in pathogenesis
- Presents with erythematous follicular comedones, papules, and pustules on face
- Histology: follicular pustules with neutrophils

### **Sclerema Neonatorum**

- Onset usually within first week of life; form of panniculitis in severely ill, premature infants; often fatal
- Presents with diffuse woody hardening of skin; spares genitalia, palms, and soles
- Histology: needle-shaped clefts with necrotic adipocytes with little surrounding inflammation

### **Subcutaneous Fat Necrosis of the Newborn** (Figure 2.1C)

- Onset within first weeks of life; localized form of sclerema neonatorum in healthy infants
- Presents with indurated subcutaneous nodules favoring cheeks, shoulders, back, buttocks, and thighs
- Associated with hypothermia, perinatal hypoxemia (from preeclampsia, meconium aspiration, etc.), hypoglycemia
- Calcification may occur;  $\pm$  profound hypercalcemia with resolution, so prudent to monitor calcium levels until 1 month after full resolution of lesions
- Histology: panniculitis with prominent inflammatory infiltrate, needle-shaped clefts and fat necrosis

### **Pedal Papules of Infancy**

- Soft, non-painful papules involving heels



**Figure 2.1**

**A: Neonatal pustular melanosis\***

**B: Neonatal cephalic pustulosis**

(Reprint from Boekhout T, Gueho-Kellerman E, Mayser P, Velegraki A. *Malassezia and the Skin*. New York, NY: Springer; 2010)

**C: Subcutaneous fat necrosis\***

\*Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine; 2005

**Seborrheic Dermatitis** (Figure 2.2A)

- Onset typically 1 week after birth; lasts several months, mostly resolves by 1 year of age
- Presents with ill-defined erythematous patches with waxy scale over scalp (“cradle cap”), ± axillae and groin; lesions may appear psoriasiform

**Miliaria Crystallina (MC) or Miliaria Rubra (MR)**

- Onset within first few weeks of life; due to obstructed sweat glands and associated with ↑ temperature (i.e., occlusion)
- Presents with clear vesicles favoring head, neck, and upper trunk (MC) or erythematous papules/vesicles grouped in intertriginous areas or occluded areas (MR)

**Aplasia Cutis Congenita (ACC)** (Figure 2.2B, C)

- Onset before birth; localized defect in epidermis, dermis and/or fat; variable appearance, typically along midline
- Presents with erosion, ulceration, scar, or membranous defect (ovoid lesion covered by an epithelial membrane)
- Hair collar sign: ring of dark long hair encircling lesion; ± marker of underlying neural tube defect
- Typically isolated abnormality, but may be associated with developmental anomalies or following disorders:

<b>Bart Syndrome</b>	ACC of <b>lower extremities</b> + <b>epidermolysis bullosa</b> (dominant dystrophic)
<b>Adams–Oliver Syndrome</b>	ACC on scalp (with skull ossification defect) + extensive <b>CMTC</b> + <b>limb defects</b> (reductions, syndactyly) + cardiac abnormalities
<b>Seitles Syndrome</b>	<b>Bilateral temporal ACC</b> + abnormal eyelashes, “ <b>leonine</b> ” facies, upward-slanting eyebrows

**Cutis Marmorata Telangiectatica Congenita (CMTC)**

- Onset at birth; typically improves with age
- Presents with blanching reticulated vascular pattern on trunk/extremities with segmental distribution
- Associated anomalies in 1/2 of patients (varicosities, nevus flammeus, macrocephaly, ulceration, hypoplasia, and/or hypertrophy of soft tissue and bone)

**Sucking Blister**

- Onset at birth or soon after; due to sucking
- Presents with solitary blister (hand, wrist, or lip)

Congenital Infections of the Newborn (see Table 2-1)

Differential Diagnosis of ‘Diaper Dermatitis’ (see Table 2-2)



**Figure 2.2**

**A:** Seborrheic dermatitis

**B:** ACC, cicatricial

(Courtesy of Dr. Michelle B. Bain)

**C:** ACC, bullous

(Courtesy of Dr. Michelle B. Bain)



**Table 2-1 Congenital Infections of the Newborn**

Infection	Clinical Findings	Extracutaneous Findings	Important Points
<b>Cytomegalovirus (CMV)</b>	Petechiae, purpura, vesicles, and “ <b>blueberry muffin</b> ” lesions  <b>Blueberry muffin lesions:</b> red-blue papules/nodules due to dermal erythropoiesis	Intrauterine growth retardation, chorioretinitis, intracranial calcification	⇒ Leading infectious cause of <b>deafness</b> and mental retardation ⇒ Typical findings on histology: <b>enlarged endothelial cells with intranuclear inclusions</b>
<b>Herpes Simplex Virus (HSV)</b>	Localized or disseminated skin lesions (vesicles, erosions, scarring)	Encephalitis (predilection for <b>temporal</b> lobes), multi-organ failure, ocular infection	⇒ Majority HSV2, 85% acquired perinatally ⇒ <b>50–75% mortality</b> if left untreated
<b>Rubella</b>	“ <b>Blueberry muffin</b> ” lesions	Cataracts, deafness, congenital heart disease, CNS findings (microcephaly, hydrocephaly), hepatosplenomegaly (HSM)	⇒ 50% chance of deafness ⇒ Severe birth defects if within <b>first 16 weeks</b> of pregnancy ⇒ Non-immune pregnant woman transfer the virus to the fetus
<b>Toxoplasmosis</b>	“ <b>Blueberry muffin</b> ” lesions favoring the trunk	Ocular abnormalities (chorioretinitis, blindness), CNS abnormalities (deafness, mental retardation, seizures), thrombocytopenia, intracranial calcification	
<b>Varicella</b>	<b>Cicatricial</b> skin lesions	Ocular abnormalities (chorioretinitis, cataracts), cortical atrophy, psychomotor retardation, hypoplastic limbs	⇒ Greatest risk in <b>first 20 weeks</b> ⇒ 2% risk of embryopathy in women with infection within first two trimesters
<b>Syphilis, Early Congenital</b>	Syphilitic pemphigus, <b>rhagades</b> (radial furrows/fissures in perioral area, turn into parrot lines), papulosquamous macules/papules (like secondary syphilis)	<b>Snuffles</b> (rhinitis, secondary to ulcerated mucosa), enlarged lymph nodes and spleen, neurosyphilis  Be able to differentiate early and late congenital syphilis findings	⇒ Early congenital syphilis occurs from <b>birth to 2 years of age</b> ⇒ Only congenital syphilis may show <b>bullous lesions</b> ⇒ Papulosquamous lesions common in the diaper area
<b>Syphilis, Late Congenital</b>	Hutchinson’s teeth, Higoumenakis sign, mulberry molars, saddle nose, saber shins, parrot lines and furrows	Interstitial keratitis, gummas along long bones/skull, tabes dorsalis, generalized paresis	⇒ Includes permanent sequelae of early congenital signs ⇒ Higoumenakis sign: congenital thickening of the medial aspect of the clavicle

**Table 2-2 Differential Diagnosis for Diaper Dermatitis**

Entity	Clinical Findings
Candidal Dermatitis	Bright red patches with pustules and satellite papules, $\pm$ intertriginous involvement ( <b>including scrotum</b> ), $\pm$ thrush
Irritant Dermatitis	Poorly demarcated erythematous plaques, <b>sparing inguinal folds</b>
Seborrheic Dermatitis	Typical salmon-colored scaly patches and plaques involving the scalp, groin, and other intertriginous areas
Psoriasis	Sharply demarcated bright pink to red plaques <b>involving inguinal creases</b> , minimal scale; most common psoriatic presentation in infants
Allergic Contact Dermatitis	Rare in infants, $\pm$ related to topical preparations or foods
Atopic Dermatitis	Increased incidence of diaper dermatitis in atopic patients
Miliaria	Clear vesicles or erythematous papules/pustules due to blocked eccrine ducts from heat or humidity in diaper area
Granuloma Gluteale Infantum	Red to violaceous granulomatous nodules over the vulva, perianal area, buttocks, $\pm$ scrotum; due to irritation, occlusion, candidal infection
Perianal Pseudoverrucous Nodules	Erythematous nodules and papules in children with fecal incontinence
Acrodermatitis Enteropathica	<p>Erythematous crusted patches/plaques with flaccid bullae in perineal, periorificial, and distal extremities; due to <math>\downarrow</math> <b>zinc level</b> (also <math>\downarrow</math> <b>alkaline phosphatase</b> as zinc-dependent); may occur in following settings:</p> <ol style="list-style-type: none"> <li>1. <b>Premature</b> infants (poor absorption and <math>\uparrow</math> requirement of zinc) when <b>weaned off breast milk</b> (which has adequate zinc level)</li> <li>2. Inherited form (AR) manifests when <b>weaned off breast milk</b></li> <li>3. Healthy infants if low zinc level in maternal milk</li> <li>4. Acquired form if malabsorption or inadequate nutrition</li> </ol>
Cystic Fibrosis	Resembles acrodermatitis enteropathica, also due to zinc deficiency $\pm$ pedal edema, failure to thrive, infections and malabsorption
Multiple Carboxylase Deficiency	Both resemble acrodermatitis enteropathica (periorificial dermatitis); treatment for both forms (listed below) is <b>biotin</b>
Biotin Deficiency	<ol style="list-style-type: none"> <li>1. Neonatal form: AR, <b>holocarboxylase synthetase deficiency</b>, <math>\pm</math> erythroderma with alopecia, <u>fatal</u> if not treated</li> <li>2. Juvenile form: <b>biotinidase deficiency</b>, <math>\pm</math> seizures, alopecia, hearing loss, developmental delay</li> </ol>
Langerhans Cell Histiocytosis	Yellow-brown crusted papules with purpura in <b>seborrheic</b> distribution; $\pm$ systemic involvement; Langerhans cells ( <b>CD1a +, S100+</b> )
Kawasaki Disease	Tender erythema in perineal area which later desquamates
Perianal Strep	Bright red, well-demarcated perianal erythema and involving creases
Bullous Impetigo	Honey-colored crusts and flaccid bullae
Scabies	Erythematous nodules involving diaper area, $\pm$ genitalia
Congenital Syphilis	Reddish-brown papulosquamous eruption, may be <b>erosive or bullous</b>

## 2.2 CHILDHOOD INFECTIOUS DISEASES

**Table 2-3 Childhood Infections**

Disease	Exanthem	Etiology/Course
<b>Acute Hemorrhagic Edema of Infancy</b> (Finkelstein Disease)	Large circinate painful purpuric plaques involving face, ears, distal extremities → evolve into edematous targetoid lesions	<u>Etiology</u> : likely infectious (viral or bacterial) <u>Age</u> : 6 months–3 years; self-limited <b>Leukocytoclastic vasculitis</b> seen on histology May be hypersensitivity reaction to infection (medication/vaccination less likely)
<b>Erythema Infectiosum</b> (‘Slapped Cheek’ or Fifth Disease)	Bright red macular erythema over cheeks → <b>lacy eruption</b> mainly on the extremities	<u>Etiology</u> : parvovirus B19 (ssDNA) also causes hydrops fetalis; peaks in spring and winter <u>Age</u> : school-age children; self-limited Mild prodrome, 10% with arthralgias
<b>Gianotti–Crosti Syndrome</b>	Abrupt onset of skin-colored to pink-red edematous papules to cheeks, buttocks, extremities	<u>Etiology</u> : likely infectious (HBV, EBV) <u>Age</u> : 6 months–2 years; self-limited May have low-grade fever and lymphadenopathy
<b>Hand-Foot-Mouth Disease</b>	Elliptical grayish vesicles, pustules, and erosions on hands, feet, and buttocks  Oral: vesicles/erosions red base	<u>Etiology</u> : <b>coxsackievirus A16</b> (enterovirus 71 less often) <u>Age</u> : children <10 years (± adults); self-limited Fever, sore mouth, anorexia, abdominal pain; enteroviral infection may also cause myocarditis, pneumonia, meningoencephalitis
<b>Henoch–Schönlein Purpura (HSP)</b>	Purpuric macules and papules favoring <b>lower extremities and buttocks</b>	<u>Etiology</u> : possibly infectious (viral, strep) <u>Age</u> : peaks at 4–7 years (± adults); self-limited Presents 1–2 week after upper respiratory infection Arthralgias, GI bleeding, abdominal pain, nephritis with <b>hematuria</b> → <b>IgA vasculitis</b>
<b>Herpangina</b>	Exanthem: often absent  Oral: painful gray vesicles on tonsillar, palate, buccal mucosa	<u>Etiology</u> : various enteroviruses (often coxsackie group A/B and echovirus) <u>Age</u> : 3–10 years old; self-limited
<b>Kawasaki Disease</b> (Mucocutaneous Lymph Node Syndrome)	Polymorphous eruption (morbilliform, erythema multiforme-like or bullous); ± edema and erythema of distal extremities; can be generalized or localized (groin, LE)  Oral: red swollen or dry fissured lips; strawberry tongue; pharyngeal erythema	<u>Etiology</u> : unknown but likely infectious <u>Age</u> : children <5 years of age Arthritis, abdominal pain, GI symptoms <u>Complications</u> : <b>cardiac aneurysm (in ¼ of untreated patients), myocarditis, pericarditis</b> Need 5 of 6 criteria for diagnosis: rash • fever >5 days • conjunctivitis • palmoplantar erythema, edema, or desquamation • swollen lips or red tongue • cervical lymphadenopathy
<b>Measles</b> (Rubeola or First Disease)	Erythematous macules/papules over forehead, hairline, and behind the ears → spreads downward  Oral: Koplik spots (gray papules on buccal mucosa)	<u>Etiology</u> : measles virus (paramyxovirus) <u>Age</u> : unvaccinated children Prodrome: fever, cough, nasal congestion, rhinorrhea, conjunctivitis; rash appears after Koplik spots <u>Complications</u> : encephalitis, otitis media, pneumonia, myocarditis, ± subacute sclerosing panencephalitis



Table 2-3 Childhood Infections (cont'd)

Disease	Exanthem	Etiology/Course
<b>Infectious Mononucleosis</b>	Polymorphous: morbilliform (common), urticarial, petechial, or erythema multiforme-like lesions  Of note, morbilliform eruption may occur after treatment with ampicillin	<u>Etiology</u> : infectious (EBV) <u>Age</u> : children, young adults (15–25 years); self-limited  Fever, pharyngitis, fatigue, myalgias, headaches, hepatosplenomegaly, lymphadenopathy <u>Complications</u> : splenic rupture, airway obstruction, hepatitis
<b>Papular Purpuric Gloves and Socks Syndrome</b>	Erythema, edema, petechiae, and purpura on palms/soles ( $\pm$ extension to dorsal aspect), + <b>burning and pruritus</b>	<u>Etiology</u> : <b>parvovirus B19</b> <u>Age</u> : children and young adults; self-limited Mild prodromal symptoms, occurs mainly in young adults; peaks in spring
<b>Roseola</b> (Exanthem Subitum or Sixth Disease)	Circular to elliptical “rose red” macules or papules involving trunk, occasionally surrounded by white halo	<u>Etiology</u> : human herpesvirus 6 (HHV6) <u>Age</u> : 6 months–3 years <b>Sudden-onset high fever</b> ; rash begins as fever subsides <u>Complications</u> in healthy patient: mainly <b>seizures</b>
<b>Rubella</b> (German Measles or Third Disease)	Erythematous macules and papules on face $\rightarrow$ spreads acraly, accompanied by <b>tender lymphadenopathy</b> (occipital, postauricular, cervical)	<u>Etiology</u> : togavirus (ssRNA) <u>Age</u> : unvaccinated children/adults; self-limited Usually mild prodrome <u>Complications</u> : arthralgia/arthritis, hepatitis, myocarditis, pneumonia
<b>Scarlet Fever</b> (Second Disease)	Erythema of axilla, neck, chest $\rightarrow$ evolve to pink papules with erythematous background (sandpaper-like) $\rightarrow$ hand and foot desquamation (7–10 days later); <b>Pastia’s lines</b> (linear petechial streaks in body folds)  Oral: “ <b>red strawberry</b> ” tongue	<u>Etiology</u> : group A $\beta$ -hemolytic streptococci (erythrogenic toxin A, B, C) <u>Age</u> : children (1–10 years old) Extracutaneous: sore throat, headaches, chills, fever, nausea, abdominal pain, anorexia <u>Treatment</u> : PCN 10–14 days (erythromycin in PCN- allergic pts)
<b>Unilateral Laterothoracic Exanthem</b>	Morbilliform or eczematous eruption in axilla and lateral trunk with unilateral dominance ( $\pm$ bilateral involvement)	<u>Etiology</u> : likely viral <u>Age</u> : children (6 months–10 years); self-limited
<b>Varicella</b> (Chickenpox)	Pruritic, erythematous macules/papules of scalp, face $\rightarrow$ spreads to trunk and extremities, evolves into vesicles with narrow red halo (“ <b>dew drops on rose petal</b> ”), central crust or necrosis seen within lesions	<u>Etiology</u> : varicella zoster virus (VZV) <u>Age</u> : children and adults; self-limited in healthy children <u>Complications</u> in children: secondary bacterial infection  Adults with more severe presentation (pneumonia, 10–30% mortality if untreated) <b>All stages of development</b> seen simultaneously



**Figure 2.3**

**A:** Dermal hematopoiesis (Courtesy of Dr. Vandana Mehta)

**B:** Congenital syphilis (Courtesy of Dr. Paul Getz)

**C:** Congenital syphilis (Courtesy of Dr. Paul Getz)

**D:** Congenital syphilis (Courtesy of Dr. Paul Getz)

**E:** Candidiasis (Courtesy of Dr. Paul Getz)

**F:** Langerhans cell histiocytosis (Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)



**Figure 2.4**

**A: Acrodermatitis enteropathica**  
(Courtesy of Michelle B. Bain)

**B: Acrodermatitis enteropathica**  
(Courtesy of Michelle B. Bain)

**C: Gianotti-Crosti syndrome**  
(Courtesy of Dr. Michelle B. Bain)

**D: Gianotti-Crosti syndrome**  
(Courtesy of Dr. Michelle B. Bain)

**E: Varicella**

(Reprint from Abdel-Halim AW. *Passing the USMLE*. New York, NY: Springer, 2009)

**F: Papular purpuric gloves and socks syndrome**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds.. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

## 2.3 PAPULOSQUAMOUS AND ECZEMATOUS DERMATOSES

### **Psoriasis** (Figure 2.5A)

- Approximately 25% patients will have presentation before age 15
- Presents as erythematous well-demarcated plaques with micaceous scale
- Guttate psoriasis more common in children; presents with raindrop-like papules in an eruptive pattern; common triggers include strep infection, viral infection, stress, and trauma

### **Pityriasis Lichenoides (PL)**

- Two diseases forming spectrum of PL: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC)
- PLEVA: abrupt onset of erythematous papules and vesicles with crusted or necrotic centers, often involuting within weeks to months; treat with oral erythromycin, phototherapy, and/or topical corticosteroid
- PLC: reddish-brown papules with adherent scale, heals with dyschromia; more chronic course lasting months to years

### **Acropustulosis of Infancy** (Figure 2.5B)

- Onset from 6 months to 2 years; resolves by age 3
- Presents with recurrent crops of pruritic pustules on palms, soles, distal extremities (may mimic scabies infection so prudent to perform mineral oil scraping)
- Treatment: topical corticosteroid

### **Pityriasis Rubra Pilaris (PRP)** (Figure 2.5C)

- Three juvenile forms in addition to two adult forms (I/II)

<b>Classic Juvenile Form (III)</b>	Resembles classic adult form but with early onset (first 2 years of life); most resolve within 3 years; 10% cases
<b>Circumscribed Juvenile Form (IV)</b>	Lesions on extensor surfaces and present in prepubertal years; 25% cases (50% persist into adulthood)
<b>Atypical Juvenile Form (V)</b>	Similar to type III + scleroderma-like changes of hands/feet, familial basis; presents in early childhood with unrelenting course; 5% cases

### **Pityriasis Rosea (PR)**

- Self-limited papulosquamous eruption; likely viral pathogen (human herpesvirus 7, less likely HHV 6)
- Presents with initial herald patch (precedes eruption by 1–2 weeks) followed by salmon-colored oval patches and plaques with inner scale along long axis of Langer's lines of cleavage ("Christmas tree" pattern on posterior trunk); variants include inverse pattern (flexural accentuation) and papular PR (young children and darker-skinned patients)



**Figure 2.5**  
**A:** Guttate psoriasis  
**B:** Acropustulosis of infancy  
**C:** Pityriasis rubra pilaris  
 (Courtesy of Dr. Paul Getz)



**Lichen Striatus** (Figure 2.6A, B)

- Self-limited, linear inflammatory condition in children
- Presents with small erythematous scaly papules forming linear band → spreads down extremity or trunk and typically follows lines of Blaschko, ± nail involvement
- Hypopigmentation may persist for months to years after lesions resolve and points to diagnosis

**Keratosis Pilaris (KP)**

- Excessive keratinization causing horny follicular plugs on upper arms, thighs, and cheeks; associated with atopy

**KP Atrophicans**

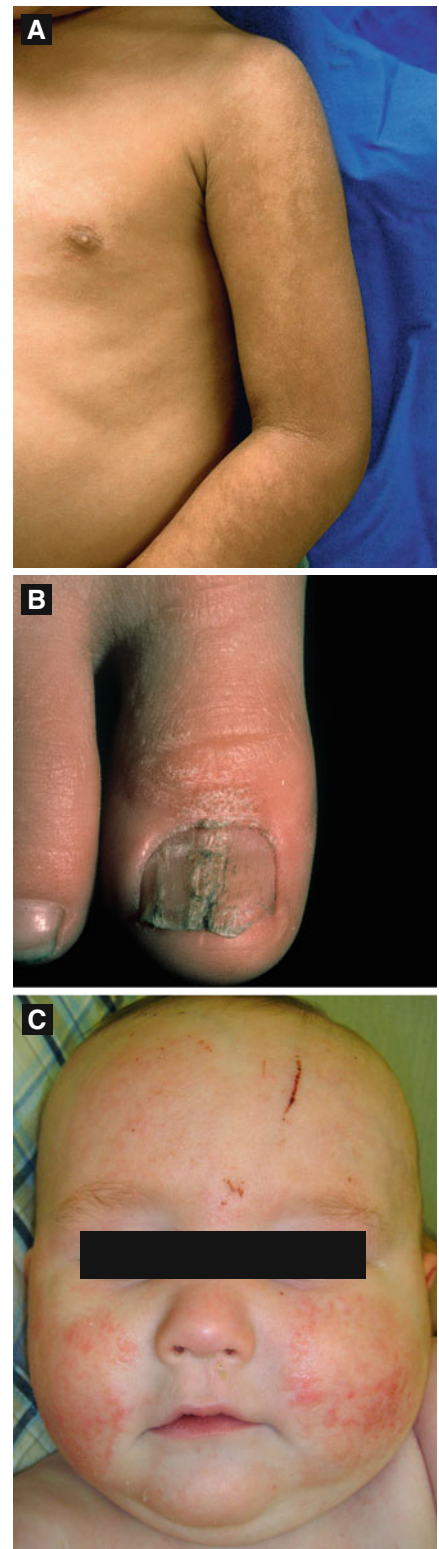
- Group of disorders in children with faulty follicular keratinization followed by atrophy and scarring
  - **KP atrophicans faciei:** erythema with follicular spiny papules of eyebrows, cheeks, and scalp; involute and leave pitted atrophic scars; term ulerythema ophyrogenes if limited to lateral 1/3 of eyebrows, associated with Noonan syndrome
  - **Atrophoderma vermiculata:** pit-like atrophic scarring of follicles on face (“honeycomb” atrophy), associated with Rombo syndrome and Down syndrome

Rombo syndrome: milia, atrophoderma vermiculata, acral cyanosis, trichoepitheliomas, multiple BCCs, hypotrichosis, alopecia

**Atopic Dermatitis (AD)** (Figure 2.6C)

- Occurs in 10–15% children, often presenting at 2–3 months of age; multifactorial pathogenesis but includes ↑ secretion of  $T_H2$  cytokines (IL-4, IL-5)
- Triad of atopy: AD, allergic rhinitis, asthma
- Few may have allergy to specific foods, which may exacerbate AD (eggs, milk, soybeans, fish, wheat, peanuts)
- Presents with eczematous lesions, xerosis, and lichenification
- Distribution varies with age
  - Infants: face, scalp, and extensors
  - Children: antecubital/popliteal fossae, neck, wrists, ankles
  - Adults: typically hands (chronic hand eczema)

Atopic patients with ↓ amount of innate antimicrobial peptides: human  $\beta$ -defensins (HBD) and cathelicidins (LL37)

**Figure 2.6****A: Lichen striatus**

(Courtesy of Dr. Michelle B. Bain)

**B: Lichen striatus**

(Courtesy of Dr. Paul Getz)

**C: Atopic dermatitis**

- **Pityriasis alba:** hypopigmented patches with minimal scale; may be only manifestation of AD (Figure 2.7A)
- Complications: keratoconus (conical deformity of cornea), eyelid dermatitis, ↑ risk of infection (impetigo, eczema herpeticum, molluscum contagiosum) (Figure 2.7B)
- Treatment: topical corticosteroid, topical calcineurin inhibitor, oral corticosteroid (short course), oral antihistamine, phototherapy

### Juvenile Plantar Dermatoses

- Typically in children with an atopic diathesis; related to increased humidity from impermeable material in shoes
- Presents with dry, scaly glazed patches with fissures involving forefoot plantar surface
- Chronic but typically self-limited

## 2.4 PIGMENTED LESIONS

### Café Au Lait Macule (CALM)

- Presents as a light to dark brown macule or patch
- Single lesion in 10–20% of normal population; multiple lesions ± associated with different genodermatoses (McCune-Albright syndrome, neurofibromatosis)

### Lentigines

- Presents as brown macules with increased number of melanocytes; no relationship to sunlight
- Multiple lentigines may be associated with the following:

<b>LEOPARD Syndrome</b>	AD, PTPN11 gene, café-noir macules, EKG changes, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, deafness
<b>Carney Complex</b> (LAMB or NAME syndrome)	AD, PRKAR1A gene, psammomatous melanotic schwannomas, cardiac/cutaneous myxomas, blue nevi, endocrine overactivity
<b>Peutz–Jeghers Syndrome</b>	AD, STK11 gene (serine threonine kinase), mucocutaneous (oral/acral) lentigines, intestinal polyposis, ± intussusception, various malignancies
<b>Laugier–Hunziker Syndrome</b>	Mucocutaneous lentigines, longitudinal melanonychia, genital melanosis
<b>Bannayan–Riley–Ruvalcaba Syndrome</b>	AD, PTEN gene, penile > vulvar lentigines, lipomas, hemangiomas



**Figure 2.7**  
**A: Pityriasis alba**  
 (Courtesy of Dr. Paul Getz)  
**B: Molluscum contagiosum**

**Ephelides (Freckles)**

- Present as light brown macules in sun-exposed areas; more prominent in children with fair skin and during summer time; onset typically within first 3 years of age
- Can be a marker for UV-induced damage if acquired
- Histology: normal number of melanocytes, increased pigment in keratinocytes

**Congenital Nevus (CN) (Figure 2.8A)**

- Onset at birth or first year typically; 1–2% of population
- Categorized as small (<1.5 cm), medium (1.5–20 cm), and large (>20 cm or 10% BSA)
- Slight ↑ risk of melanoma (highest in large CNs); 3–12% of giant (large) CNs may develop melanoma (different studies show varying percentages); axial nevi with greatest risk
- If large nevus over scalp, rule out neurocutaneous melanosis with MRI

Neurocutaneous melanosis: ↑ intracranial pressure, leptomeningeal melanoma, spinal cord compression

**Spitz Nevus (Epithelioid or Spindle Cell Nevus) (Figure 2.8B)**

- Presents as dome-shaped red-brown or tan-pink smooth surfaced papule; typically occurs within first two decades
- Pigmented, congenital, and agminated variants reported
- Histology: Kamino bodies (PAS + globules)
- Characteristic starburst dermoscopic finding in pigmented Spitz nevi

**Halo Nevus (Sutton's Nevus)**

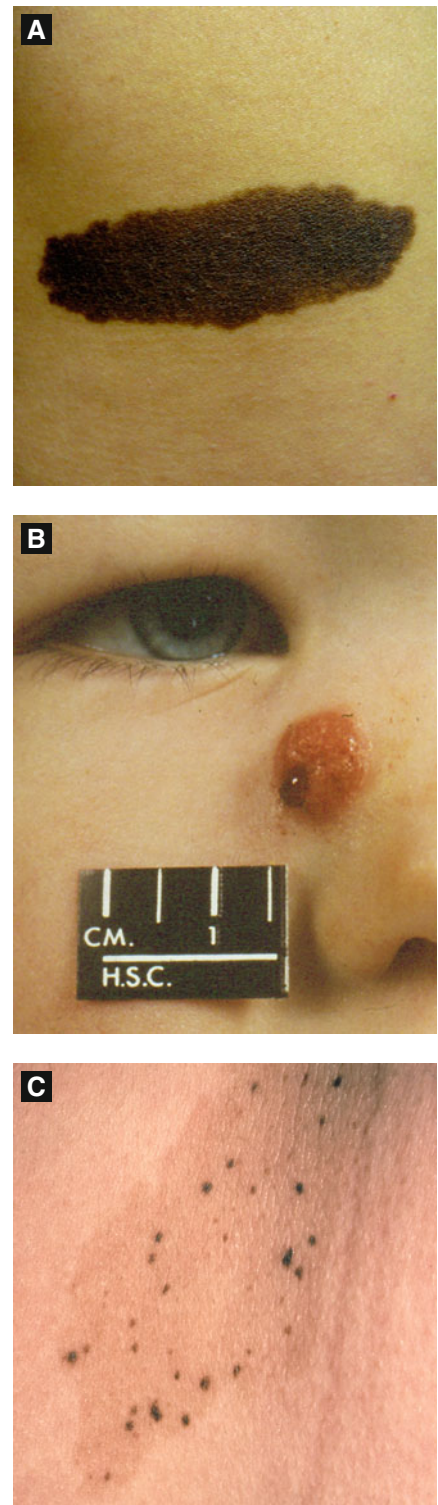
- Melanocytic nevus with surrounding hypopigmented halo in which central nevus either persists or involutes
- Typically appears in adolescence; may appear in setting of vitiligo; prudent to rule out concomitant melanoma (rare) by performing full skin exam

**Nevus Spilus (Speckled Lentiginous Nevus) (Figure 2.8C)**

- Presents as tan, regularly bordered patch with darker macules within lesion
- Melanoma rarely arises within nevus component
- Associated with phakomatosis pigmentovascularis and pigmentokeratotic (latter with organoid nevus + hemiatrophy + neurologic defects)

**Melanoma**

- 0.3–0.4% of melanomas in prepubertal children
- ↑ Risk with fair skin, blue eyes, blonde/red hair, CDKN2A or p16 mutation, xeroderma pigmentosum, dysplastic nevus syndrome, large congenital nevus, or neurocutaneous melanosis

**Figure 2.8****A: Congenital nevus****B: Spitz nevus**

(Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine; 2005)

**C: Nevus spilus**

(Courtesy of Dr. Paul Getz)



**Becker's Nevus (Becker's Melanosis)** (Figure 2.9A, B)

- Acquired unilateral lesion found in adolescent males (second or third decade) typically on shoulder, upper chest, or back
- Presents as hyperpigmented hypertrichotic patch or plaque associated with underlying smooth muscle hamartoma (arrector pili)
- Histology: ↑ melanin in epidermis, often smooth muscle hamartoma present in dermis

**Blue Nevus** (Figure 2.9C)

- Congenital or acquired (typically early childhood)
- Different types: common, cellular, and combined
- Multiple blue nevi associated with Carney complex (LAMB/NAME syndrome)
- Histology: normal epidermis, many elongated dendritic melanocytes within dermis, large amounts of melanin often seen within melanocytes

**Nevus of Ota (Nevus Fuscoceruleus Ophthalmomaxillaris, Oculodermal Melanocytosis)** (Figure 2.9D)

- Onset either near birth or during puberty
- Most common in Asian population, mainly women
- Presents as unilateral, blue-gray macules typically involving V1 and V2 distribution of trigeminal nerve
- Most common extracutaneous sites: sclera > tympanum > nasal mucosa > pharynx > palate

**Nevus of Ito (Nevus Fuscoceruleus Acromiodeltoideus)**

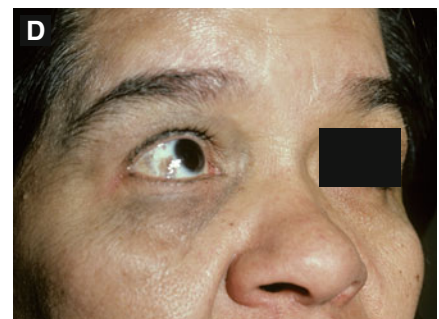
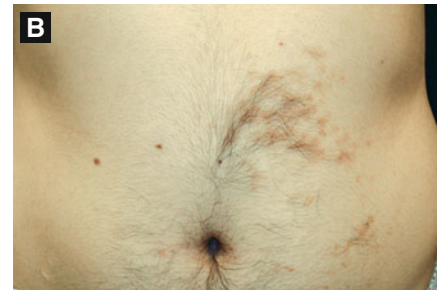
- Similar presentation to nevus of Ota but typically occurs in shoulder region (supraclavicular, scapular, and deltoid)

**Hori's Nevus (Acquired Nevus of Ota-like Macules)**

- Onset in late adolescence, mainly in Asian women
- Bilateral nevus of Ota-like macules of the zygomatic region; may be misdiagnosed as melasma

**Congenital Dermal Melanocytosis (Mongolian Spot)**

- Common in infants with pigmented skin
- Presents with blue-gray macules or patches typically over lumbosacral skin or buttocks
- If extensive, consider phakomatosis pigmentovascularis
- Histology: dendritic melanocytes situated in lower half of dermis, cells arranged parallel to epidermis

**Figure 2.9****A: Becker's nevus**

(Courtesy of Dr. Paul Getz)

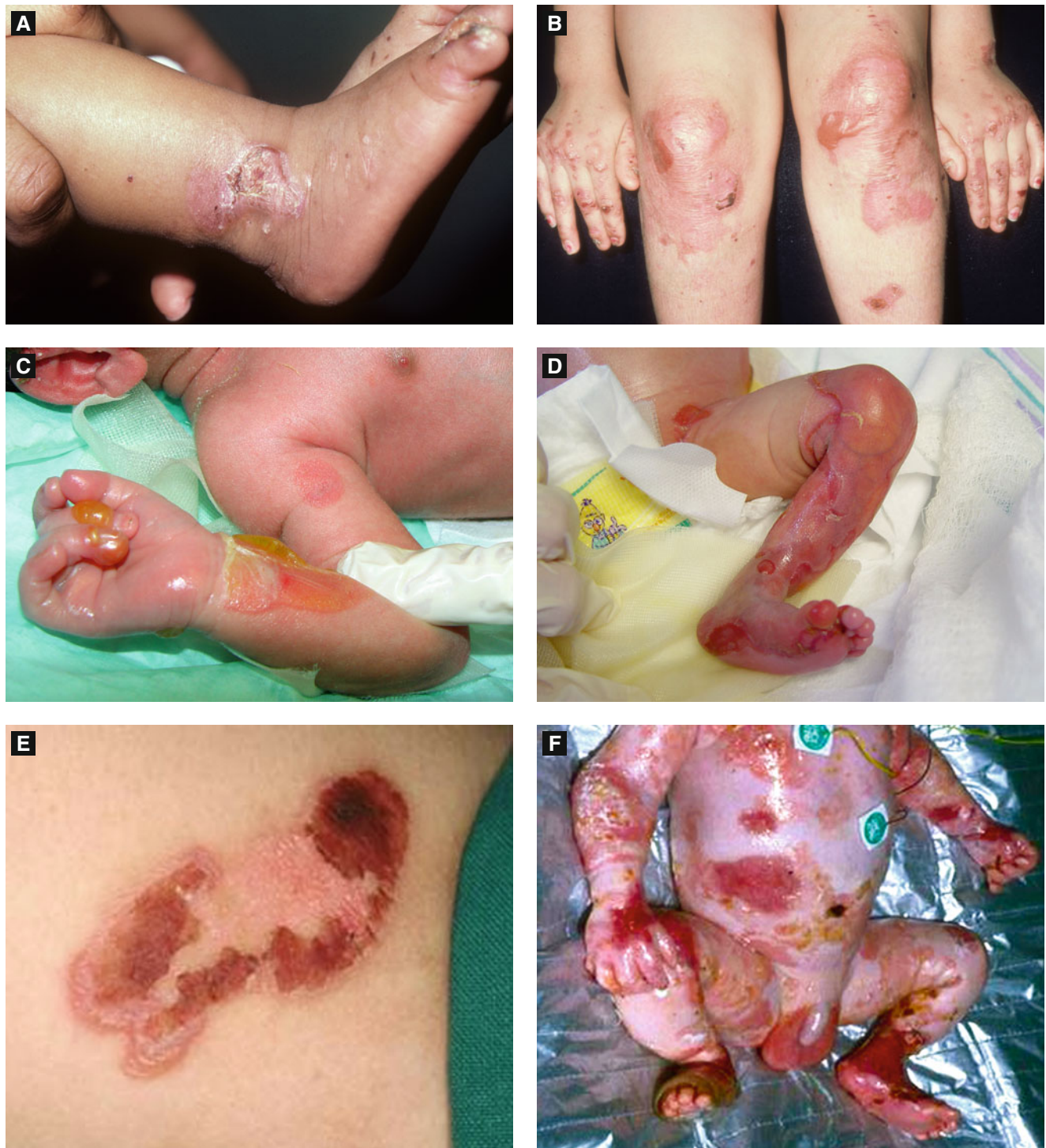
**B: Becker's nevus****C: Blue nevus** (Courtesy of Dr. Paul Getz)**D: Nevus of Ota** (Courtesy of Dr. Paul Getz)



## 2.5 BULLOUS DISEASES

Table 2-4 Epidermolysis Bullosa

EB Subtype	Inh	Gene	Clinical Features
<b>EB SIMPLEX (EBS)</b> Split: Epidermal Basal Layer			
<b>Dowling-Meara</b> (EBS Herpetiformis)	AD	K5/K14	Onset at birth, grouped or herpetiform blisters (figurate), <b>significant mucosal membrane and laryngeal/esophageal involvement (± hoarseness)</b> , nail dystrophy, confluent PPK, scarring, early death EM: <b>clumped tonofilaments</b> in basal keratinocytes
<b>Weber-Cockayne</b> (Localized)	AD	K5/K14	Onset typically childhood/adolescence, palmoplantar bullae/erosions, heal without scarring
<b>Koebner</b> (Generalized)	AD	K5/K14	Generalized bullae at birth, PPK, nail dystrophy, mucosal erosions, heals <b>without scarring</b>
<b>EBS Muscular Dystrophy</b>	AR	<b>Plectin</b>	Widespread bullae at birth, <b>muscular dystrophy</b> , scarring, hair/nail/tooth/oral disease, early death
<b>EBS Mottled Pigmentation</b>			Resembles localized and generalized EBS + <b>reticulated hyperpigmentation over trunk</b>
<b>JUNCTIONAL EB (JEB)</b> Split: Basement Membrane (Lamina Lucida)			
<b>Herlitz</b> (EB Lethalis)  Premature termination codon	AR	<b>Laminin 5</b> (laminin-332)	Severe, widespread bullae, nonhealing <b>exuberant granulation tissue</b> (perioral, axillae, neck), enamel defects, absent nails, mucosal involvement (respiratory/GI tract with hoarseness), early death
<b>Non-Herlitz</b> (Generalized Atrophic Benign EB or GABEB)	AR	Laminin 5 or BPAG2 (BP180)	Widespread bullae at birth, <b>heal with atrophic scars</b> , mild oral involvement, <b>scarring alopecia</b> , nail dystrophy, improves with time
<b>JEB with Pyloric Atresia</b>	AR	<b>α6β4 integrin</b>	Severe congenital blistering, hydronephrosis, <b>pyloric atresia</b> , mucosal erosions
<b>DYSTROPHIC EB (DEB)</b> Split: Dermal (Sublamina Densa)			
<b>Hallopeau-Siemens</b> Recessive DEB (RDEB-HS)  Premature termination codon	AR	<b>Type VII collagen</b>	Severe widespread bullae at birth, heals with atrophic scarring (on hands/feet → <b>“mitten deformity”</b> ), milia, nail dystrophy, mucosal strictures, <b>oral, esophageal, cutaneous SCCs</b>
<b>Non-Hallopeau-Siemens</b> (RDEB-nHS)	AR	Type VII collagen	Skin changes localized to acral bony prominences, Hallopeau-Siemens symptoms but less severe
<b>Cockayne-Touraine</b> (DDEB-CT)	AD	Type VII collagen	Bullae mainly over extremities, heal with milia/atrophic scars/keloids, nail dystrophy
<b>Pasini Variant</b> (DDEB-P)	AD	Type VII collagen	Similar to Cockayne subtype + albo-papuloid lesions ( <b>white perifollicular papules, slowly enlarge</b> )



**Figure 2.10**

**A:** EB simplex (Weber-Cockayne) (Courtesy of Dr. Paul Getz)

**B:** Dominant dystrophic EB (Cockayne-Touraine) (Courtesy of Dr. Paul Getz)

**C:** Recessive dystrophic EB

**D:** Recessive dystrophic EB

**E:** EB simplex (Dowling-Meara) (Reprint from Laimer M et al. *Epidermolysis bullosa hereditaria. Monatsschrift Kinderheilkunde Zeitschrift für Kinder und Jugendmedizin.* 2008; 156 (2);110–21)

**F:** EB simplex (Dowling-Meara) (Reprint from Has C et al. *Hereditäre Blasen bildende Hauterkrankungen. Der Hautarzt.* 2004; 55(10);920–30)



**Chronic Bullous Disease of Childhood** (Figure 2.11A)

- Blistering disorder with onset typically before age 5
- Target antigen: 97 kDa Ag (LAD-1 or LABD97): cleaved ectodomain of BPAG2
- Presents with annular and herpetiform bullae favoring extensor surfaces/groin (“crown of jewels” configuration)
- Histology: subepidermal bullae with neutrophils in dermal papillae (similar to dermatitis herpetiformis)
- Treat with dapsone or sulfapyridine

**Neonatal Pemphigus**

- Presents in infants whose mothers have pemphigus vulgaris; due to passive transfer of maternal IgG to fetus
- Self-limited; resolves within few weeks of birth

**Hailey–Hailey Disease (Familial Benign Chronic Pemphigus)**

(Figure 2.11B)

- AD, ATP2C1 gene (encodes Golgi-associated Ca<sup>2+</sup> ATPase hSPCA1), results in abnormal intracellular calcium signaling; onset typically second to third decade
- Presents with flaccid vesicles initially on erythematous base over intertriginous areas, ruptures easily, and gives rise to macerated or crusted erosions
- Histology: extensive epidermal acantholysis “dilapidated brick wall”

Think of “Hailey’s Comet” to remember ATP2 C 1

**2.6 EPIDERMAL, APPENDAGEAL, AND DERMAL TUMORS****Epidermal Nevus (EN)** (Figure 2.11C)

- Hamartoma of epidermis and papillary dermis; onset typically at birth (± adolescence, rare in adulthood)
- Presents as hyperpigmented papillomatous papules and plaques along lines of Blaschko
- Ichthyosis hystrix: extensive bilateral systematized lesions
- **ILVEN** (inflammatory linear verrucous epidermal nevus): erythematous scaly plaque along lines of Blaschko; not associated with any neurologic defects
- **Epidermal nevus syndrome** (Schimmelpenning syndrome): sporadic; epidermal nevus, underlying CNS, ocular, cardiac, and skeletal defects, biopsy to r/o epidermolytic hyperkeratosis (EHK)

Of note, if biopsy of EN shows EHK, the patient may be at risk with offspring with full-blown EHK

**Figure 2.11**

**A:** Chronic bullous disease of childhood  
(Courtesy of Dr. Michelle B. Bain)

**B:** Hailey–Hailey disease  
(Courtesy of Dr. Paul Getz)

**C:** ILVEN (Courtesy of Dr. Paul Getz)

### ***Nevus Sebaceus*** (Figure 2.12A, B)

- Presents as solitary yellow-orange slightly raised plaque typically on scalp or face; plaque typically thickens and becomes more verrucous or pebbly during childhood
- Mutation in PTCH gene has been reported (deletion)
- Benign tumors (trichoblastoma, syringocystadenoma papilliferum) and malignant tumors (BCC < 1% cases) can arise within lesion

### ***Basal Cell Carcinoma***

- Seen in children with xeroderma pigmentosum (XP) and basal cell nevus syndrome (BCNS)

### ***Squamous Cell Carcinoma***

- Seen in children with XP, dystrophic EB, and albinism

### ***Pilomatricoma (Calcifying Epithelioma of Malherbe)***

- Onset typically in childhood
- Presents as solitary firm, skin-colored to faint blue papule or cyst on face or upper trunk
- Histology: anucleate cornified cells (“ghost” or “shadow” cells), calcification seen in late lesions
- Multiple pilomatricomas may be associated with myotonic dystrophy (β-catenin defect)

### ***Trichoepithelioma*** (Figure 2.12C)

- Benign adnexal neoplasm usually appearing in childhood
- Presents as skin-colored translucent papules (usually multiple) along the nasolabial folds or periorbital regions
- Multiple lesions in Brooke–Spiegler syndrome (trichoepitheliomas, cylindromas, spiradenomas)

### ***Angiofibroma (Fibrous Papule)***

- Skin-colored firm papule on face
- Multiple lesions associated with tuberous sclerosis (once known as adenoma sebaceum) with onset in early to mid-childhood



**Figure 2.12**

A: Nevus sebaceus\*

B: Nevus sebaceus\*

C: Trichoepitheliomas\*

\* Courtesy of Dr. Paul Getz

**Neurofibroma (NF)** (Figure 2.13A)

- Presents as skin-colored, soft or rubbery papulonodule with positive “buttonhole” sign (easily invaginated)
- Commonly seen as solitary lesion; multiple lesions associated with neurofibromatosis
- Plexiform NF considered pathognomonic for NF1, malignant transformation in 2–13%

**Connective Tissue Nevus** (Figure 2.13B, C)

- Also known as shagreen patch (tuberous sclerosis) collagenoma, elastoma, or dermatofibrosis lenticularis disseminata (latter in Buschke–Ollendorff syndrome)
- Onset at birth or early childhood; likely hamartoma
- Presents as firm, solitary, or multiple skin-colored papules, nodules, or plaques

**Infantile Digital Fibroma** (Figure 2.13D)

- Onset within 1 year of age
- Presents as multiple firm, smooth dome-shaped nodules on dorsolateral fingers/toes (sparing thumb and great toe)
- Benign with spontaneous regression within 2–3 years typically; high local recurrence rate with surgical excision
- Histology: eosinophilic intracytoplasmic perinuclear inclusions within spindle cells

**Infantile Myofibromatosis (Congenital Generalized Fibromatosis)**

- Rare, onset at birth or within first 2 years
- Presents as one or more firm, rubbery skin-colored to purple papulonodules on head, neck, or trunk
- Two types: localized with no visceral involvement, good prognosis; visceral involvement with high mortality

**Fibrous Hamartoma of Infancy**

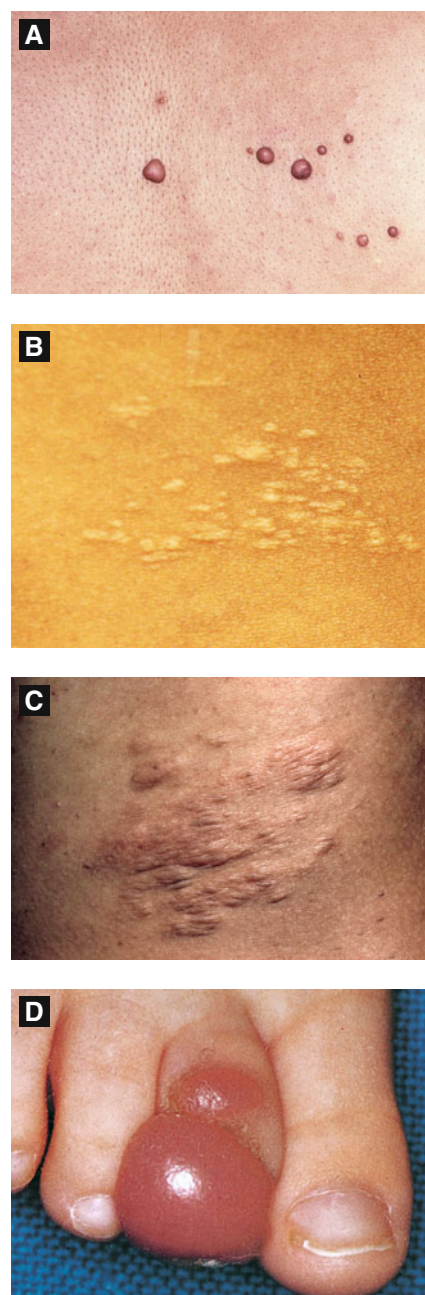
- Onset at birth or within first year of life
- Presents as painless, solitary skin-colored subcutaneous nodule typically involving axilla, shoulder, or upper arm (less likely groin area)
- Treat with local excision

**Fibromatosis Colli**

- Infiltration of fibrous tissue involving the lower third of the sternocleidomastoid muscle at birth
- Typically spontaneous remission within few months

**Juvenile Hyaline Fibromatosis**

- Due to mutation in capillary morphogenesis protein 2
- Multiple firm papules and nodules involving the face, extremities, and scalp; hypertrophic gums and disfigurement with flexion contractions

**Figure 2.13****A: Neurofibromas**

(Courtesy of Dr. Paul Getz)

**B: Connective tissue nevus**(Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine, 2005)**C: Connective tissue nevus**

(Courtesy of Dr. Paul Getz)

**D: Infantile digital fibroma**(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)



**Juvenile Xanthogranuloma (JXG)** (Figure 2.14A, B)

- Non-Langerhans cell histiocytosis with Touton giant cells; onset typically within first year of life
- Two types: micronodular (small, multiple) or macronodular (larger size, few in number)
- Presents as single or multiple firm, pink-red papulonodules with yellow hue on head/neck > trunk/upper extremities
- Regression typically seen in children (not in adults)
- 0.5% with ocular involvement: glaucoma, hyphema (may rarely result in blindness)
- Association with NF1 and juvenile myelomonocytic leukemia (JMML)

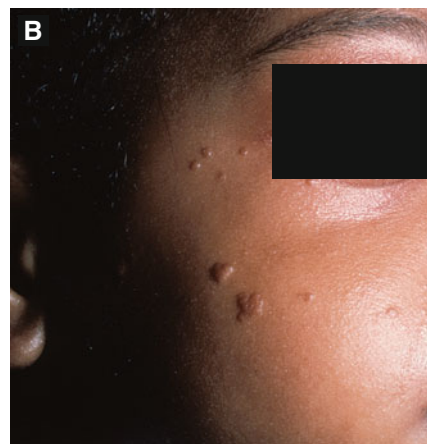
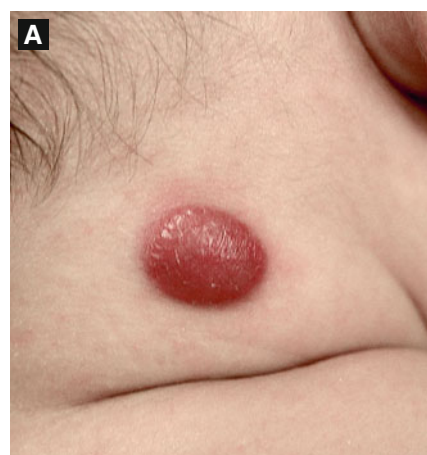
**Langerhans Cell Histiocytosis (LCH)** (Figure 2.14C)

- Clonal proliferative disease of Langerhans cells (comma-shaped nuclei, S100+, CD1a+, intracytoplasmic Birbeck granules seen on EM), four overlapping syndromes
- Current classification by number of organ systems involved (single vs. multisystem), but historically grouped as follows:

<b>Letterer–Siwe Disease</b>	<ul style="list-style-type: none"> <li>– Multisystem involvement, (acute disseminated form); onset typically before 2 years of age</li> <li>– Small, pink papules, pustules, vesicles with scale/crust/petechiae in seborrheic distribution</li> </ul>
<b>Hand–Schüller–Christian Disease</b>	<ul style="list-style-type: none"> <li>– Onset between 2 and 6 years of age</li> <li>– Typical triad: diabetes insipidus, bone lesions, exophthalmos</li> <li>– Osteolytic bone lesions (cranium)</li> </ul>
<b>Eosinophilic Granuloma</b>	<ul style="list-style-type: none"> <li>– Onset in older children, localized LCH variant</li> <li>– Asymptomatic granulomatous lesions involving bone (cranium), spontaneous fractures</li> </ul>
<b>Congenital Self-Healing Reticulohistiocytosis</b>	<ul style="list-style-type: none"> <li>– Onset at birth or soon after, limited to skin; also known as Hashimoto-Pritzker disease</li> <li>– Widespread, red-brown papulonodules</li> <li>– Self-healing within weeks to months</li> </ul>

**Benign Cephalic Histiocytosis**

- Self-limited histiocytosis (S100 negative non-LCH); onset within first 3 years of life
- Presents with small red-brown macules and papules on face, spreading to neck and ears > trunk and arms; spontaneous resolution after months or years

**Figure 2.14**

**A: Juvenile xanthogranuloma**  
(Courtesy of Dr. Michelle B. Bain)

**B: Juvenile xanthogranuloma**  
(Courtesy of Dr. Paul Getz)

**C: LCH**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**Dermoid Cyst** (Figure 2.15A)

- Seen typically in infants along embryonic fusion plane
- Presents as discrete, subcutaneous nodule commonly around eyes or nasal root
- Histology: lined by stratified squamous epithelium (with granular layer) containing appendageal elements
- CT/MRI should be performed to rule out connection to CNS before excision

**Mastocytosis** (Figure 2.15B, C)

- Spectrum of disorders with mast cell hyperplasia in skin and other organs
- Childhood mastocytosis – onset before puberty (50% before age 2), c-kit alteration (proto-oncogene, tyrosine kinase subfamily); several forms in children:

<b>Solitary Mastocytoma</b>	<ul style="list-style-type: none"> <li>– Tan to brown, minimally infiltrated plaque or nodule; spontaneous resolution over months</li> <li>– Positive Darier sign</li> </ul>
<b>Urticaria Pigmentosa (UP)</b>	<ul style="list-style-type: none"> <li>– Onset early childhood, may occur in adults</li> <li>– Hyperpigmented to pink pruritic macules or papules on trunk; positive Darier sign</li> <li>– Variant: bullous UP</li> </ul>
<b>Diffuse Cutaneous Mastocytosis</b>	<ul style="list-style-type: none"> <li>– Doughy or boggy skin texture with lichenification and yellow hue</li> <li>– Extreme pruritus, friction may cause bullae</li> <li>– Systemic symptoms: bronchospasm, diarrhea</li> </ul>
<b>Telangiectasia Macularis Eruptiva Perstans (TMEP)</b>	<ul style="list-style-type: none"> <li>– Persistent eruption of macules and papules with red-brown hue</li> <li>– Rare in childhood</li> </ul>

- Avoid mast cell degranulators: aspirin, alcohol, opiates, quinine, polymyxin B sulfate, amphotericin B, tubocurarine, scopolamine

**2.7 TUMORS OF FAT, MUSCLE AND BONE****Lipoma**

- If located over lumbosacral region at birth, consider underlying spinal dysraphism (incomplete closure of mesenchymal, osseous, and nervous tissue of the spine) → perform MRI

Associated syndromes with lipomas: Bannayan–Riley–Ruvalcaba syndrome, Gardner syndrome, MEN I

**Figure 2.15****A: Dermoid cyst**

(Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine; 2005)

**B: Urticaria pigmentosa**

(Courtesy of Dr. Michelle B. Bain)

**C: Urticaria pigmentosa**

(Courtesy of Dr. Paul Getz)

### Cutaneous Calcification

- **Solitary nodular calcification:** benign nodule in infants typically from heel sticks
- **Osteoma cutis:** idiopathic or associated with Albright's hereditary osteodystrophy
- **Superficial calcified nodule:** solitary firm nodule on scalp or face (ears) of children

## 2.8 VASCULAR DISORDERS

### Hemangiomas and Vascular Malformations

Hemangiomas are vascular tumors arising in infancy with true cellular proliferation, which eventually regress. Vascular malformations represent errors in vascular morphogenesis (dysplastic vessels) without true cellular proliferation and without regression.

Vascular Tumors	Vascular Malformations
Infantile and Congenital Hemangiomas	Capillary Malformation (slow flow): <i>Port-Wine Stain (Nevus Flammeus)</i>
Kaposiform Hemangioendothelioma	Venous Malformation (slow flow): <i>Cavernous Hemangioma, Phlebectasia</i>
Pyogenic Granuloma	Lymphatic Malformation (slow flow): <i>Lymphangioma (Lymphangioma Circumscriptum Cystic Hygroma, Cavernous Lymphangioma)</i>
Tufted Angioma	Arteriovenous Malformation (fast flow): <i>Cirroid Aneurysm</i>
Congenital Hemangiopericytoma	Combined Malformation (slow or fast flow)

### A. VASCULAR TUMORS

#### Hemangioma of Infancy (Figure 2.16A)

- Benign vascular tumor presenting soon after birth (first few weeks after life)
- More common in premature infants, 15% have multiple lesions with higher risk for visceral involvement, GLUT1 positive (endothelial marker, useful in differentiating from malformation)
- Precursor lesion: pink or bruised macule or patch with surrounding telangiectasias
- **Superficial hemangioma** (strawberry hemangioma) situated in the superficial dermis and bright red in color during the proliferative phase
- **Deep or cavernous hemangioma** (located deep dermis and/or subcutis) presents as blue-purple mass with normal overlying skin,  $\pm$  bruit
- Involution: 30% by age 3, 50% by age 5, 70% by age 7, 90% by age 9
- Complications: ulceration (most common), anatomic distortion with interference of normal function, high-output congestive heart failure (greater risk with visceral hemangiomas, especially if in liver)
- Regionally significant hemangiomas: periocular (obstruct vision and cause ophthalmologic complications), beard region (clue for laryngeal hemangiomatosis with airway obstruction), segmental hemangioma over lumbosacral area (MRI of spine to r/o GU/GI/spinal/skeletal abnormalities), nasal tip (textural changes and scarring)



## PHACES

- Posterior fossa malformation, **h**emangioma, **a**rterial anomalies, **c**ardiac defect, **c**oarctation of the aorta, **e**ye abnormalities, **s**ternal defects, and **s**upraumbilical raphe
- Hemangiomas tend to be plaque-like on the face involving more than one dermatome
- Most common posterior fossa malformation: Dandy–Walker malformation

## Diffuse Neonatal Hemangiomatosis

- Cutaneous and visceral hemangiomas; liver hemangioma may be complicated by obstructive jaundice
- If multiple cutaneous hemangiomas, perform ultrasound, urinalysis, stool guaiac, CBC to r/o systemic involvement
- If no visceral involvement → benign neonatal hemangiomatosis
- ↑ Mortality with systemic form due to high-output cardiac failure, GI bleeding, and respiratory compromise

## Tufted Angioma (Figure 2.16B)

- Onset during infancy or early childhood
- Presents as ill-defined red-brown plaque or patch over neck or upper trunk; plaque slowly extends with time (typically does not regress)

## PELVIS Syndrome

- Perineal hemangioma, external genital malformation, lipomyelomeningocele, vesicorenal anomalies, imperforate anus, and skin tag

## Pyogenic Granuloma (Figure 2.16C)

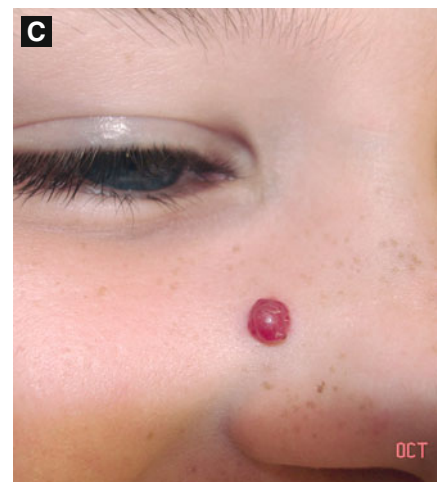
- Presents as rapidly growing, friable red papule of skin or mucosa with frequent ulceration
- Common in children and young adults
- Associated with antecedent trauma, pregnancy, oral medications (retinoids, imatinib, EGFR inhibitors)

## Kaposiform Hemangioendothelioma (Figure 2.17A)

- Usually onset before age 2
- Presents as vascular macules, plaques, nodules, or bulging indurated masses
- Associated with Kasabach–Merritt syndrome → consumptive coagulopathy with thrombocytopenia (platelet sequestration) and purpura; deep-seated tumors (i.e., retroperitoneal) likely to cause above syndrome

## Glomeruloid Hemangioma

- Distinct vascular proliferation in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin lesions)
- Presents as firm, red-purple papules over trunk or extremities



**Figure 2.16**  
**A: Hemangioma**  
 (Courtesy of Dr. Michelle B. Bain)  
**B: Tufted angioma**  
**C: Pyogenic granuloma**

## B. VENOUS MALFORMATIONS

### Capillary Malformation (Nevus Flammeus, Port-Wine Stain, PWS) (Figure 2.17B)

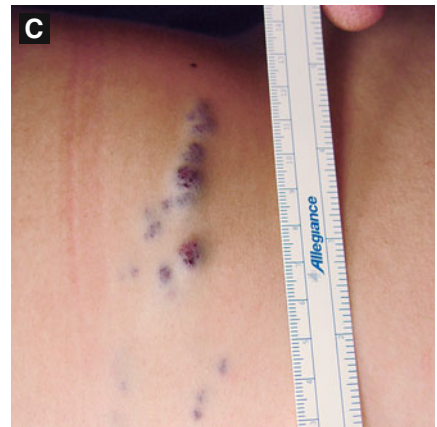
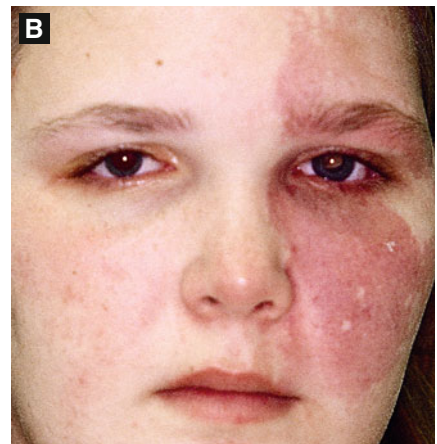
- Presents as a well-demarcated erythematous patch or plaque that grows in proportion to general growth of the body; does not spontaneously recede (unlike “salmon patches” over forehead, glabella, nose/philtrum, nape or eyelid which typically disappear by age 3)
- Facial PWS follows sensory CN V distribution (V1–V3); over time, skin changes from pink to deep purple and thickens with ↑ nodularity and pyogenic granulomas
- GLUT1 negative
- PWS can be seen with combination of epidermal or melanocytic abnormalities: phakomatosis pigmentovascularis (see below)
- Associated syndromes: Sturge–Weber syndrome, Klippel–Trénaunay syndrome, Proteus syndrome

### Phakomatosis Pigmentovascularis

- Type 1: PWS + epidermal nevus
- Type 2: PWS + dermal melanocytosis ± nevus anemicus
- Type 3: PWS + nevus spilus ± nevus anemicus
- Type 4: PWS + dermal melanocytosis + nevus spilus ± nevus anemicus

### Glomangioma (Glomuvenous Malformation) (Figure 2.17C)

- Arises in children and adolescents; may be sporadic or inherited (autosomal dominant with incomplete penetrance; defect in glomulin gene)
- If solitary lesion (glomus tumor), onset typically in adulthood with subungual location
- Presents as soft pink to deep blue papules or nodules in segmental distribution; tender to palpation, ± attacks of pain with pregnancy or menstruation
- Histology: resembles vascular malformation but vessels lined with one or more rows of cuboidal glomus cells



**Figure 2.17**

**A: Kaposiform hemangioendothelioma (in Kasabach-Merritt)**

(Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine; 2005)

**B: Port-wine stain** (Reprint from Abel-Halim AW. *Passing the USMLE*. New York, NY: Springer; 2009)

**C: Glomangiomas** (Courtesy of Dr. Michelle B. Bain)

**Angiokeratoma (Figure 2.18A)**

- Ectasias of dermal capillaries
- Presents as a dark red to purple papule; either solitary or multiple; distribution varies by type

<b>Solitary Angiokeratoma</b>	Single red to dark brown papule usually on the lower extremity
<b>Angiokeratoma Circumscriptum</b>	Large verrucous papules or plaques typically involving the extremity, onset in early childhood/infancy
<b>Angiokeratoma of Mibelli</b>	Rare, presents as several 1–5 mm dark, red-gray papules over acral areas with verrucous surface
<b>Angiokeratoma Corporis Diffusum (Fabry Disease)</b>	Numerous tiny telangiectatic red papules associated with hereditary lysosomal storage disease, XLR, $\alpha$ -galactosidase A deficiency
<b>Angiokeratoma of the Scrotum (Fordyce)</b>	Multiple small red-violaceous papules studding the scrotum, less often the vulva, onset in adulthood

**Lymphangioma**

- Uncommon congenital malformation of the lymphatic system; either superficial (lymphangioma circumscriptum) or deep-seated (cavernous lymphangioma)
- Lymphangioma circumscriptum: multiple translucent vesicles with clear lymph fluid (resembling frog spawn)
- Cystic hygroma (variant of cavernous lymphangioma): deep-seated large translucent soft mass typically over neck, axilla, or lateral chest

**C. TELANGIECTASIAS****Spider Angioma (Spider Nevus) (Figure 2.18B, C)**

- Common acquired lesion seen in children and adults
- Comprised of central arteriole with radiating thin walled vessels; temporary obliteration seen with compression
- Presents as bright red papule with central papule surrounded by distinct radiating vessels
- Multiple lesions associated with liver disease, pregnancy, and estrogen therapy

**Angioma Serpiginosum**

- Onset typically within first two decades of life
- Presents as small, red punctate asymptomatic macules in serpiginous pattern typically over extremity



**Figure 2.18**  
**A:** Angiokeratoma  
**B:** Spider angioma  
**C:** Spider angioma



## 2.9 GENODERMATOSES

### X-Linked Recessive

CHAD'S Kinky WIFE, CHANdra

- **C:** Chronic Granulomatous Disease
- **H:** Hunter Disease
- **A:** Anhidrotic (Hypohidrotic) Ectodermal Dysplasia (Christ-Siemens-Touraine)
- **D:** Dyskeratosis Congenita
- **S:** SCID
- **Kinky:** Kinky Hair Disease (Menkes Disease)
- **W:** Wiskott–Aldrich Syndrome
- **I:** Ichthyosis, X-linked
- **F:** Fabry Disease
- **E:** Ehlers–Danlos Syndrome (type V and IX)
- **C:** Chondrodysplasia Punctata (not Conradi–Hünemann type)
- **H:** Hypohidrotic ED with Immunodeficiency
- **A:** Agammaglobulinemia, Bruton
- **N:** Lesch–Nyhan Syndrome

Of note, type IX EDS (occipital horn syndrome) is NOT part of the revised EDS classification (since it is NOT due to a collagen defect) and type V is classified as “other” in EDS classification

### X-Linked Dominant

BIG ChOMP

- **B:** Bazex Syndrome (do not confuse with acrokeratosis paraneoplastica {Bazex syndrome})
- **I:** Incontinentia Pigmenti (Bloch–Sulzberger Syndrome)
- **G:** Goltz Syndrome (Focal Dermal Hypoplasia)
- **C:** CHILD Syndrome
- **h:** –
- **O:** Oro-Facial-Digital Syndrome
- **M:** MIDAS Syndrome (micrognathia, dermal aplasia, sclerocornea)
- **P:** Chondrodysplasia Punctata (Conradi–Hünemann type)

## A. SYNDROMES WITH DEFECTIVE DNA REPAIR

### Xeroderma Pigmentosum (XP) (Figure 2.19A, B)

- AR, due to defect in DNA repair
- Seven complementation groups (A–G) and one XP variant described, each encoding different proteins in the nucleotide excision repair (NER) pathway (except XP variant)
- Presents with marked photosensitivity, early onset of all major skin malignancies, exaggerated sunburn following minimal sun exposure, solar lentigines by age of 2, ocular abnormalities (photophobia, keratitis, corneal opacification, vascularization), neurologic abnormalities (progressive deafness)
- XP variant (mutation in DNA polymerase): no neurologic abnormalities
- DeSanctis–Cacchione syndrome (Gr. A): severe neurologic abnormalities (MR, deafness, ataxia)

### Cockayne Syndrome

- AR, defective excision repair: unable to repair cyclobutane pyrimidine dimer products after irradiation, ↑ chromosomal breaks
- Two complementation groups: **CS-A (ERCC8)** and **CS-B (ERCC6)**
- Presents with photosensitivity, mental retardation, cachectic dwarfism, peripheral neuropathy, sunken eyes, prominent ears, “salt and pepper” retinitis pigmentosa, dental caries, thinning hair, basal ganglia calcification

**COCKAYNE** – eight letters (ERCC8), Cachectic dwarfism, **O**cular (salt/pepper RP), Cataracts, **A**void sun, **E**ars (“mickey mouse”)



**Figure 2.19**

**A: Xeroderma pigmentosum**  
(Courtesy of Dr. Michelle B. Bain)

**B: Xeroderma pigmentosum**  
(Courtesy of Dr. Michelle B. Bain)

**C: Rothmund–Thomson**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

**Trichothiodystrophy (PIBIDS)**

- AR, mutation in gene ERCC2 (XPD protein) and ERCC3 (XPB protein) in NER pathway, sulfur deficiency in hair
- PIBIDS: **P**hotosensitivity (50%), **I**chthyosis (variable severity), **B**rittle hair (alternating bright and dark bands known as “tiger tail,” flattened hair shafts like a ribbon), **I**ntellectual impairment, **D**ecreased fertility, **S**hort stature, **R**eceding chin, **P**rotruding ears

**Trichothiodystrophy – Tiger Tail abnormality**

**Bloom Syndrome**

- AR, BLM gene mutation, RecQ protein-like two (RecQL2, some sources say RecQL3 {Spitz}), DNA helicase family, mutation results in ↑ spontaneous sister chromatid exchanges, breakage, and rearrangements
- Presents with photodistributed erythema/telangiectasias over cheeks within first few weeks of life, short stature, normal intelligence, immune deficiency causing chronic respiratory/GI infections, ↓ fertility, ↓ IgM/IgA, high-pitched voice
- ↑ Risk cancer: leukemia, lymphoma, GI adenocarcinoma

**BLooM** – 2 O's (RecQL2)

**Butterfly** rash, **L**eukemia, **i**mmune deficiency, ↓ **IgM**

**Rothmund–Thomson Syndrome (Poikiloderma Congenitale)**

(Figure 2.19C)

- AR, RECQL4 (DNA helicase)
- Presents with photodistributed erythema and vesicles on face in first few months of life, evolves into poikiloderma and extends to buttocks and extremities, premalignant acral keratoses, alopecia, cataracts, hypoplastic thumbs/radii/ulnae, ↑ risk osteosarcoma, normal intelligence

**Rothmund Thomson** – **R**educed **T**humbs

**ROTH** (4 letters) – RecQL4

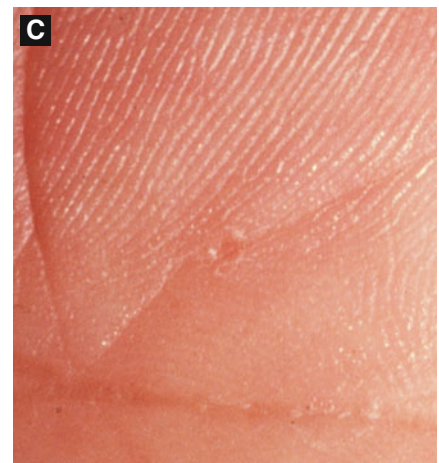
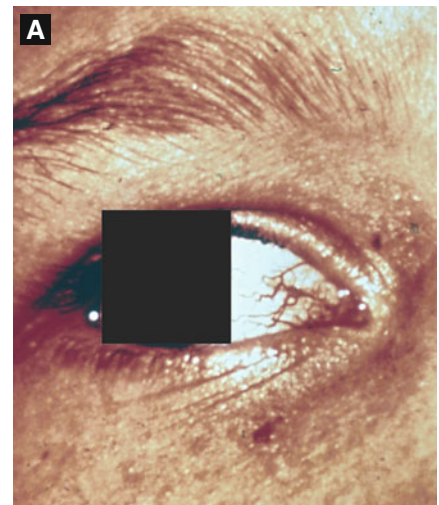
**Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome)**

- Two forms: XLR and AD
- XLR, DKC1 gene mutation, encodes protein dyskerin (interacts with telomerase), ↑ sister chromatid exchanges
- AD, hTR (human telomerase RNA component) and hTERT (human telomerase reverse transcriptase) mutations
- Cutaneous poikiloderma (face, trunk, thighs), nail dystrophy (atrophy, pterygium), pre-malignant leukoplakia (buccal mucosa most common), frictional bullae, palmoplantar hyperhidrosis
- Bone marrow failure with anemia, thrombocytopenia, or pancytopenia → major cause of mortality
- ↑ CA: mucosal SCC, Hodgkin's lymphoma, AML

**DYSkeRaTOSis** – **DYS**trophy (nails), **mR**, **T**hrombocytopenia, **O**ral pre-malignant leukoplakia, **S**un avoidance (poikiloderma)

**Ataxia-Telangiectasia Syndrome (Figure 2.20A)**

- AR, ATM gene mutation, inability to repair chromosomal strand breaks, sensitivity to ionizing radiation



**Figure 2.20**

**A: Ataxia-Telangiectasia**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**B: Basal cell nevus syndrome\***

**C: Palmar pits (BCNS)\***

\*Courtesy of Dr. Paul Getz



- Presents first with ataxia (2–3 years old) → telangiectasias on bulbar conjunctivae (spreads to cheeks/ears), premature aging (atrophic/sclerotic face), ↓ Purkinje fibers in cerebellum
- Defects in cellular and humoral immunity (↓ IgA, IgG, IgE), severe and frequent sinopulmonary infections, ↑ lymphoreticular malignancy, ↑ breast CA

### Fanconi Syndrome

- AR, ↑ chromosomal breakage
- Presents with diffuse hyperpigmentation, multiple CALMs, pancytopenia, ↑ SCC, ↑ solid organ CA, ↑ leukemia, hypoplasia of radius/thumb

FanCONi – CONe-shaped defect (hypoplasia of distal structures – radius/thumb)

## B. SYNDROMES OF TUMOR SUPPRESSION

### Basal Cell Nevus Syndrome (Gorlin Syndrome) (Figure 2.20B, C)

- AD, PTCH (PATCHED) gene, inhibits sonic hedgehog signaling (unbound PTCH inhibits Smoothened (SMO) signaling; when inactivating mutation occurs in PTCH → repression of SMO removed → constitutive activation of Gli and downstream targets)
- Presents with numerous BCCs, palmar/plantar pits, odontogenic keratocysts of jaw, characteristic facies (frontal bossing, hypertelorism), cataracts, glaucoma, bifid ribs, calcification of falx cerebri, agenesis of corpus callosum, ovarian fibromas, medulloblastoma, meningioma

### Neurofibromatosis, Type I (Von Recklinghausen Disease)

(Figure 2.21A–C)

- AD, NF-1 gene, encodes neurofibromin (tumor suppressor protein)
- Criteria: two or more of the following six:

Six or more CALMs or two or more neurofibromas or one plexiform neurofibroma	Cafe au lait macule (CALM): > 0.5 cm prepubertal, >1.5 cm postpubertal
Axillary or inguinal freckling (Crowe's sign)	
Optic glioma	
Lisch nodules	
Sphenoid wing dysplasia or thinning cortex of long bone	
First degree relative with NF	

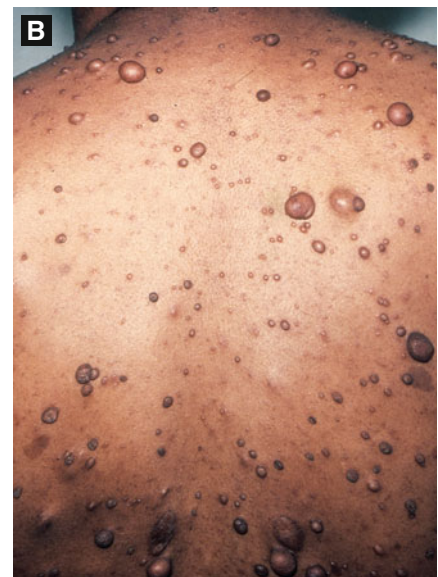
- ↑ Risk of tumors: optic glioma, malignant peripheral nerve sheath tumor, neurosarcoma, juvenile myelomonocytic leukemia, rhabdomyosarcoma
- ± Hypertension, mental retardation (MR), seizures, kyphoscoliosis, endocrine disorder (precocious puberty, acromegaly, thyroid/parathyroid abnormalities)

### Neurofibromatosis, Type II (Bilateral Acoustic NF)

- AD, NF-2 gene, encodes merlin/schwannomin
- Diagnosis requires bilateral CNVII masses OR first degree relative AND either unilateral CN VIII mass OR two of the following: schwannoma, optic glioma, meningioma, juvenile posterior subcapsular opacity

### Carney Syndrome (NAME or LAMB Syndrome)

- AD, PRKAR1A gene



**Figure 2.21**

**A:** CALMs\*

**B:** Neurofibromatosis\*

**C:** Neurofibromatosis\*

\*Courtesy of Dr. Paul Getz

- Presents with ephelides, blue nevi, lentigines, cutaneous myxomas (flesh-colored papules over ears, eyelids, nipples), primary pigmented nodular adrenocortical disease (results in Cushing syndrome)
- Tumors: testicular tumors, pituitary GH-secreting tumors, psammomatous melanotic schwannomas

**NAME:** nevi, atrial myxoma, myxoid tumors, ephelides

**LAMB:** lentigines, atrial myxomas, mucocutaneous myxomas, blue nevi

### Muir–Torre Syndrome

- AD, mutation in MLH1 and MSH2 (DNA mismatch repair genes) causing microsatellite instability
- Multiple sebaceous neoplasms and keratoacanthomas
- ↑ Risk of colon adenocarcinoma, less common GU, lung, breast or heme malignancy

**Muir–Torre:** think of “**more**” and more sebaceous neoplasms

### Tuberous Sclerosis (Figure 2.22A, B)

- AD, TSC1 gene mutation (hamartin), and TSC2 (tuberin)
- Ash-leaf macules (earliest finding), facial angiofibromas, connective tissue nevi (shagreen patch), fibromas (gingival and subungual), CALMs, dental enamel pits
- Renal angiomyolipomas, retinal hamartomas, seizures, pulmonary lymphangiioleiomyomatosis, cortical tubers, cardiac rhabdomyoma

### Cowden Syndrome (Multiple Hamartoma Syndrome) (Figure 2.22C)

- AD, PTEN gene mutation, encodes tyrosine phosphatase protein, mutation causes cell proliferation
- Trichilemmomas (smooth to verrucous small papules on face), “cobblestone” appearance of the mucosa including tongue (oral papillomas), acral keratotic papules
- ↑ Breast fibroadenoma, ↑ CA: breast, thyroid follicular; GI polyps

**COW**den – trichile**MOO**mas; other PTEN syndromes: Lhermitte–Duclos and Bannayan–Zonana syndrome

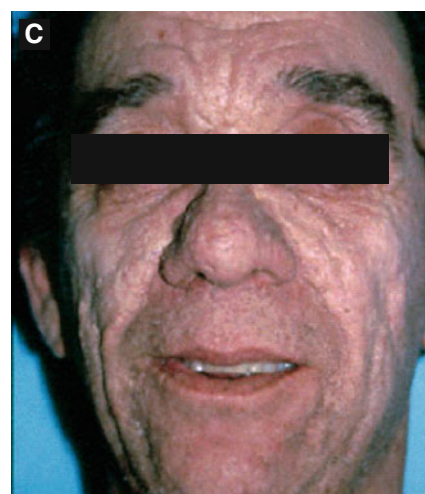
### Multiple Endocrine Neoplasia (MEN)

<b>Type 1</b> (Wermer Syndrome)	– AD, <b>MEN1</b> mutation (menin: tumor suppressor)
	– Angiofibromas, collagenomas, lipomas, CALMs
	– Pituitary, parathyroid, pancreatic tumors
<b>Type 2a</b> (Sipple Syndrome)	– AD, <b>RET</b> mutation (tyrosine kinase receptor)
	– <b>Lichen or macular amyloidosis</b> , hemangiomas, genital lentigines, hamartomas, lipomas
	– Parathyroid tumor, <b>thyroid medullary carcinoma</b> , pheochromocytoma
<b>Type 2B</b> (Multiple Mucosal Neuroma Syndrome)	– AD, <b>RET</b> mutation
	– <b>Multiple mucosal neuromas</b> , thickened lips
	– <b>Thyroid medullary carcinoma</b> , pheochromocytoma, marfanoid habitus, diffuse ganglioneuromatosis (megacolon, diarrhea)

MEN 1: 3 P’s (pituitary, pancreas, parathyroid)+CALMs

MEN 2**A**: Amyloidosis (“sipple” syndrome: think “rippled” macular amyloid)

MEN2**B**: Blubbery lips due to mucosal neuromas



**Figure 2.22**

**A:** Angiofibromas in TS

(Courtesy of Dr. Michelle B. Bain)

**B:** Koenen tumor in TS

(Courtesy of Dr. Paul Getz)

**C:** Cowden syndrome (Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)



**Bannayan–Riley–Ruvalcaba Syndrome**

- AD, PTEN mutation
- Genital lentigines, hamartomas, lipomas, hemangiomas, mental retardation, macrocephaly

**Bannayan** – think of an old **banana** with dark spots on the outside resembling lentigines

**LEOPARD Syndrome (Multiple Lentigines Syndrome)**

- AD, PTPN11 gene mutation, encodes tyrosine phosphatase Shp2
- **L**entigines, **E**CG abnormalities, **o**cular hypertelorism, **p**ulmonic stenosis, **a**bsent genitalia, **r**etarded growth and **d**eafness
- Multiple lentigines at birth/early infancy (sun exposed and protected areas, including genitalia, hands, feet)

**Peutz–Jeghers Syndrome** (Figure 2.23A)

- AD, STK11/LKB1 gene mutation, encodes serine-threonine kinase tumor suppressor
- Hyperpigmented macules on lip/oral mucosa/fingers (starts in infancy/early childhood) and intestinal polyposis (± bleeding, intussusception)
- ↑ GI adenocarcinoma, ↑ other solid organ malignancies

PeuTz(S) Jeghers – Threonine Serine kinase

**Gardner Syndrome**

- AD, APC gene encoding tumor suppressor gene (ras proto-oncogene)
- Cutaneous epidermoid cysts, osteomas (mandible, maxilla), supernumerary teeth, odontomas, fibromas, congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- Tumors: GI adenocarcinoma (inevitable), osteochondromas, thyroid papillary carcinoma, hepatoblastoma, adrenal adenomas

**Gardner** – birds **CHiRP** in the **GARDen**

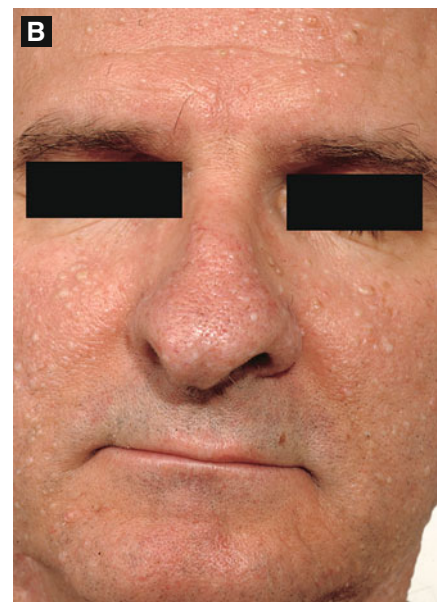
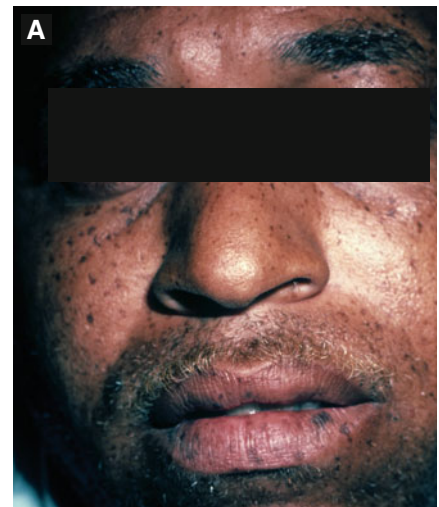
**Birt–Hogg–Dubé Syndrome** (Figure 2.23B, C)

- AD, BHD gene (encodes folliculin)
- Multiple fibrofolliculomas, trichodiscomas, acrochordons on the face, scalp, neck, and upper trunk
- Associated with renal cell carcinoma, medullary carcinoma of thyroid, spontaneous pneumothorax (multiple pulmonary cysts)

Birt **HOGG** Dube – think of a **hog** with rough textured skin (because of fibrofolliculomas and trichodiscomas)

**Dysplastic Nevus Syndrome**

- AD, CDKN2A (p16 tumor suppressor gene, inhibits cyclin-dependent kinase 4 [CDK4])
- Dysplastic nevi, melanoma, pancreatic CA, astrocytomas



**Figure 2.23**

**A: Peutz–Jeghers syndrome**

(Courtesy of Dr. Paul Getz)

**B: Birt–Hogg–Dubé syndrome\***

**C: Birt–Hogg–Dubé syndrome\***

(\*Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)



## C. SYNDROMES WITH PREMATURE AGING

### Werner Syndrome (Adult Progeria) (Figure 2.24A)

- AR, RECQL2 gene mutation (WRN gene), encodes RecQ DNA helicase, genomic instability (↑ aging/cancer)
- Normal growth until second decade, then short stature/thin limbs, graying of hair in adolescence, central obesity, pinched facial expression, beaked nose, micrognathia, high-pitched voice, mottled hyperpigmentation, sclerodermoid changes, cataracts, diabetes mellitus, premature atherosclerosis, chronic leg ulcers
- ↑ Soft tissue sarcomas, osteosarcomas, SCCs

Werner – tWo (recql2)

### Progeria (Hutchinson–Gilford Syndrome) (Figure 2.24B)

- AD, lamin A gene mutation (LMNA), encodes lamin A and lamin C (nuclear envelope protein)
- Markedly premature aging (median lifespan 12 years), large appearing cranium, frontal bossing, prominent scalp veins, beaked nose, micrognathia, “plucked bird” appearance, loss of subcutaneous tissue, sclerodermoid skin; alopecia, high pitched voice, average intelligence, severe premature coronary atherosclerosis

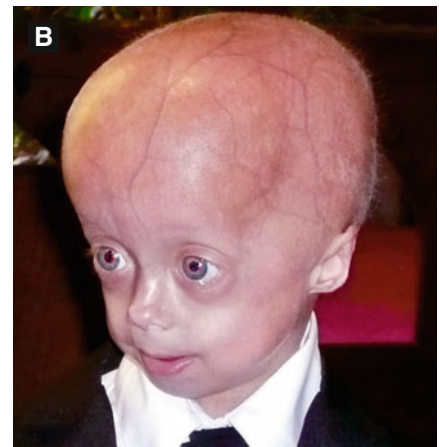
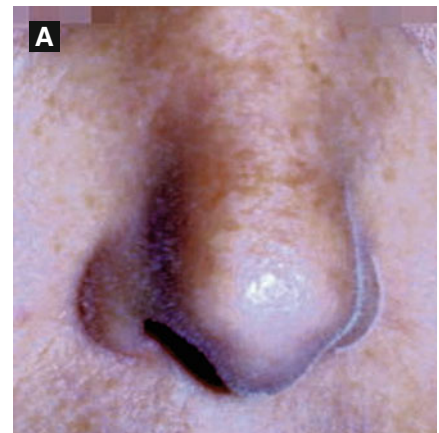
## D. DISORDERS WITH IMMUNODEFICIENCY

### Familial Chronic Mucocutaneous Candidiasis (FCMC)

- Recurrent, progressive candidal infections (skin, nails, and mucosa) presenting with recurrent oral thrush, nail dystrophy, crusted cutaneous plaques

### Hyper-IgE Syndrome (Job Syndrome) (Figure 2.24C)

- AD, mutation in gene encoding STAT3 (signal transducer and activator of transcription 3), AR (gene encoding tyrosine kinase 2 TYK2)
- ↑ IgE levels, peripheral eosinophilia, cold abscesses, coarse facies, eczematous dermatitis, lung abscesses, pneumonia, retained primary teeth, pneumatocele, otitis media, osteopenia with recurrent fractures



**Figure 2.24**

**A: Werner syndrome**

(Reprint from Baykal C, Yazganoglu KD. *Dermatological Diseases of the Nose and Ears*. Berlin: Springer; 2010)

**B: Progeria**

(Courtesy of the Howard family)

**C: Hyper-IgE syndrome**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

**Wiskott–Aldrich Syndrome (WAS)**

- XLR, WASP gene, encodes WAS protein (controls assembly of actin filaments)
- Thrombocytopenia and platelet dysfunction (since birth) → petechiae and ecchymoses of skin, epistaxis, melena, hematemesis, hematuria
- Atopic dermatitis (face, scalp, flexures), excoriated areas with crust/petechiae, recurrent bacterial infections
- Hepatosplenomegaly, lymphadenopathy, ↑ lymphoma (non-Hodgkin's lymphoma)
- Death from infections > hemorrhage > malignancy
- Treatment: bone marrow transplantation

**Severe Combined Immunodeficiency (SCID)**

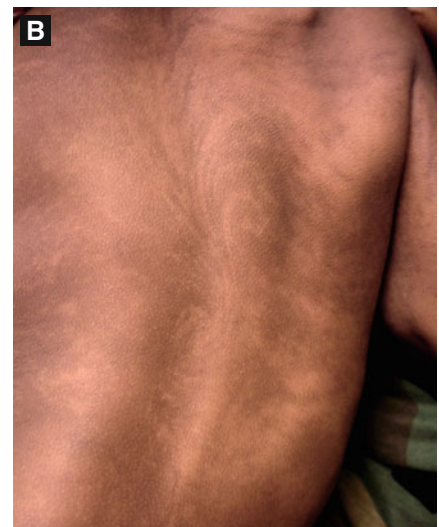
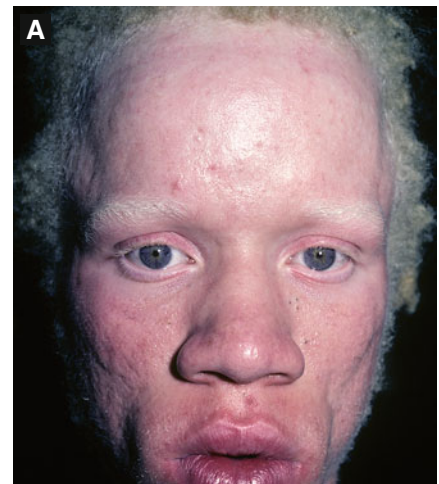
- XLR, deficiency of  $\gamma$  chain of IL2 receptor (IL2RG); AR, defect in tyrosine kinase JAK3 or adenosine deaminase (ADA); heterogeneous disorders with severely impaired humoral and cellular immunity
- Deficiency or total absence of circulating lymphocytes

**Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED)**

- AR, AIRE gene (autoimmune regulator gene) mutation
- Candidal infections, endocrinopathy (thyroid/parathyroid abnormality, diabetes mellitus, hypoadrenocorticism), cutaneous and other autoimmune disorder (alopecia areata, vitiligo, pernicious anemia)
- Varied cutaneous presentations: seborrheic-like dermatitis or morbilliform eruption, recurrent candidiasis and bacterial infections, chronic diarrhea, failure to thrive

**E. DISORDERS OF PIGMENTATION****Oculocutaneous Albinism (OCA) (Figure 2.25A)**

Type	Inheritance/Defect	Clinical
OCA, Type 1a (Tyrosinase-negative)	AR <b>TYR</b> (Tyrosinase enzyme deficiency)	No melanin in skin/hair/eyes, white hair (over time may turn slightly yellow), milky white-pink skin, blue-gray eyes, <b>amelanotic nevi</b> (pink), extreme UV sensitivity, ↑ skin CA, nystagmus, strabismus, ↓ visual acuity
OCA, Type 1b (Yellow mutant)	AR <b>TYR</b>	↓ Tyrosinase activity, little or no pigment at birth, develop some pigment over time, milder eye findings
OCA, Type 2 (Tyrosinase-positive)	AR <b>P gene</b> (↓ Eumelanin synthesis)	<b>Most common</b> OCA, broad clinical phenotype (minimal to moderate dilution), pigmented nevi develop over time, light brown hair/skin
OCA, Type 3 (Rufous)	AR <b>TYRP-1</b> (Tyrosinase-related protein 1)	Light brown hair/skin, blue or brown irides, nystagmus, ↓ visual acuity

**Figure 2.25****A: Oculocutaneous albinism**

(Courtesy of Dr. Paul Getz)

**B: Hypomelanosis of Ito****C: Incontinentia pigmenti**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009)

### Chédiak–Higashi Syndrome

- AR, LYST/CHS1 gene mutation (lysosomal trafficking regulator), defect in vesicle trafficking
- Giant intracytoplasmic granules (involving melanocytes, platelets, leukocytes)
- Onset at infancy: oculocutaneous albinism with immunologic deficiency, silvery metallic hair (clumps of melanin microscopically), recurrent infections, easy bruising, progressive neurologic deterioration, giant lysosomal granules, slate-gray skin color
- “Accelerated phase”: pancytopenia, lymphohistiocytic infiltration of reticuloendothelial system
- Treatment: stem cell transplantation

### Hermansky–Pudlak Syndrome

- AR, HPS gene mutation (lysosomal transport protein) or AP3B1 (formation of vesicles and protein trafficking)
- Oculocutaneous albinism, hemorrhagic diathesis (absent dense bodies in platelets) with epistaxis, ecchymosis, menorrhagia, pulmonary fibrosis, granulomatous colitis, renal failure, cardiomyopathy

### Griselli Syndrome

- AR, myosin Va or Rab27a gene mutation, encodes GTPase (ras family)
- Variable pigmentary dilution, silvery metallic hair, recurrent pyogenic infections, pancytopenia, neurologic involvement, immunodeficiency
- Uneven clumps of melanin in medulla on microscopy of hair; giant melanosomes NOT seen

### Hypomelanosis of Ito (Figure 2.25B)

- Sporadic, due to somatic mosaicism
- Onset at birth/early childhood, whorled/linear/patchy hypopigmentation (unilateral or bilateral) following lines of Blaschko;  $\pm$  CNS, eye, skeletal, or tooth abnormalities

### Incontinentia Pigmenti (Bloch–Sulzberger Syndrome) (Figure 2.25C)

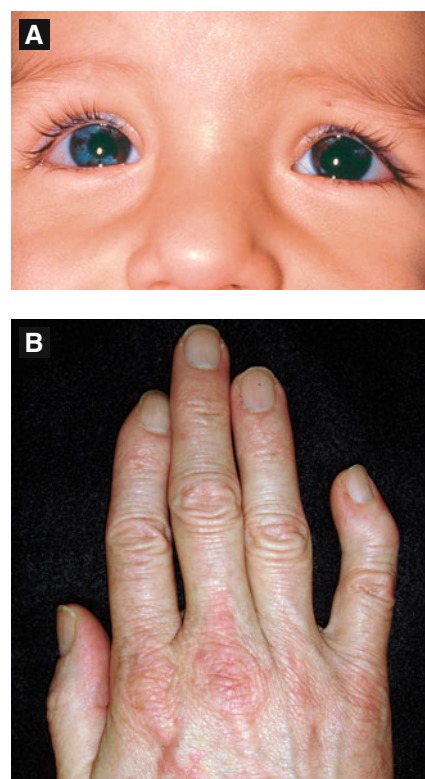
- XLD, NEMO gene mutation (NF $\kappa$ B essential modulator), lethal in males; cutaneous lesions follow lines of Blaschko
- Four stages:

<b>Vesicular stage:</b> vesicles in linear/whorled streaks
<b>Verrucous stage:</b> hyperkeratotic linear plaques
<b>Hyperpigmented:</b> linear/whorled hyperpigmentation
<b>Hypopigmented:</b> hypopigmented thin streaks

- Associated with patchy scarring alopecia, absent or peg-shaped teeth, CNS abnormalities (seizures, delayed psychomotor development), ocular disease (retinal vascular abnormalities, blindness)

### Piebaldism

- AD, c-kit gene mutation (proto-oncogene, tyrosine-kinase receptor family), defective melanocyte migration and development
- White forelock, irregularly shaped leukoderma favoring anterior trunk, extremities, forehead (leukoderma spares hands, feet, hips, shoulders), otherwise healthy



**Figure 2.26**

**A: Waardenburg syndrome**

(Reprint from Levine N, Levine CC. *Dermatologic Therapy: A–Z Essentials*. New York: Springer; 2009.)

**B: Clinodactyly of 5th finger**



**Waardenburg Syndrome (Figure 2.26A)**

- Four types below:

Type	Inh	Defect	Clinical
WS, Type 1	AD	<b>PAX3</b> (transcription factor)	White forelock, leukoderma, <b>heterochromia iridis</b> , <b>synophrys</b> , <b>dystopia canthorum</b> (characteristic), broad nasal root, <b>deafness uncommon</b>
WS, Type 2	AD	<b>MITF</b> (transcription factor)	Similar to WS1 but dystopia canthorum absent, <b>deafness common</b>
WS, Type 3	AD	<b>PAX3</b>	Similar to WS1 + <b>upper limb abnormalities</b> (hypoplasia, syndactyly, flexion contractures)
WS, Type 4	AD AR	<b>SOX10</b> (TF) EDN3 (endothelin-3) EDNRB (endothelin receptor)	Similar to WS1 + <b>Hirschsprung disease</b> , deafness common

**F. DISORDERS WITH PIGMENTED LESIONS****McCune–Albright Syndrome (Polyostotic Fibrous Dysplasia)**

- Sporadic, GNAS 1 gene mutation, encodes  $\alpha$  subunit of Gs adenylate cyclase
- Large café-au-lait macules (geographic border), precocious puberty, pathological fractures, endocrine abnormalities (hyperparathyroidism, hyperthyroidism, acromegaly), sclerosis at base of skull

**MCC**une –Café au lait macules, pre**C**ocious puberty; do **NOT** confuse with Albright hereditary osteodystrophy (pseudohypoparathyroidism)

**Russell–Silver Syndrome (Figure 2.26B)**

- Presents with triangular facies, hemihypertrophy, clinodactyly of the fifth finger, syndactyly of second/third toes

**G. VASCULAR DISORDERS****Sturge–Weber Syndrome (SWS) (Figure 2.27A)**

- Sporadic neurologic disorder, facial PWS associated with ipsilateral ocular and leptomeningeal anomalies
- Facial PWS typically involves V1 distribution (can be more extensive or bilateral), congenital or acquired ocular abnormalities (glaucoma), neurologic abnormalities (seizures, motor dysfunction, mental retardation), intracranial “tram-track” calcification
- 10–15% patients with PWS of V1 distribution have underlying SWS

**Klippel–Trénaunay Syndrome (KTS) (Figure 2.27B, C)**

- Sporadic, vascular malformation of a limb associated with bone and soft tissue hypertrophy of the affected extremity with lymphatic and deep venous insufficiency
- Gigantism of the involved limb; may become painful and edematous, even ulcerate,  $\pm$  recurrent cellulitis

**Figure 2.27****A: Sturge–Weber syndrome**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009)

**B: Klippel–Trénaunay syndrome**

(Courtesy of Dr. Michelle B. Bain)

**C: Klippel–Trénaunay syndrome**

(Courtesy of Dr. Michelle B. Bain)

- Can also have urinary/GI vascular lesions, less frequently can have intermittent claudication, venous ulcers, lymphedema, recurrent pulmonary emboli
- If multiple arteriovenous fistulas associated with skeletal and soft tissue hypertrophy → Parkes Weber syndrome

### Proteus Syndrome

- Sporadic, mosaic mutation in PTEN
- Named after the Greek god, Proteus, who could change his shape at will (due to dramatic variation in manifestations of syndrome)
- Cutaneous findings: hyperkeratotic epidermal nevi, palmo-plantar cerebriform connective tissue nevi, capillary malformation, hemangiomas, lipomas
- Systemic findings: asymmetric growth with partial gigantism of hands/feet, hyperostoses of epiphyses and skull (especially external auditory canal), bilateral ovarian cystadenomas

### Cobb Syndrome

- Rare, nonfamilial disorder with capillary malformation on the posterior trunk in association with spinal arteriovenous malformation (most common intramedullary)
- Kyphoscoliosis common, spinal AVM can cause neurologic deficits and can affect vertebral body (pain, weakness, muscular atrophy)

### Von Hippel–Lindau Syndrome (VHL)

- AD, VHL gene (tumor suppressor)
- Bilateral retinal/cerebellar hemangioblastomas, PWS rarely of face, ↑ renal and pancreatic CA, pheochromocytoma, progressive and fatal by age 40

### Beckwith–Wiedemann Syndrome

- AD, KIP2 gene (inhibitor of G1 cyclin)
- Circular depression over rim of helices, linear earlobe crease, facial vascular malformation, macroglossia, visceromegaly, hemihypertrophy of tissue/viscera with associated Wilms tumor and hepatoblastoma

**BECK WITH** – think of a baby named BECKy WITH earlobe creases, circular depressions (ears), protruding tongue, and Wilms tumor

### Rubinstein–Taybi Syndrome (Figure 2.28A)

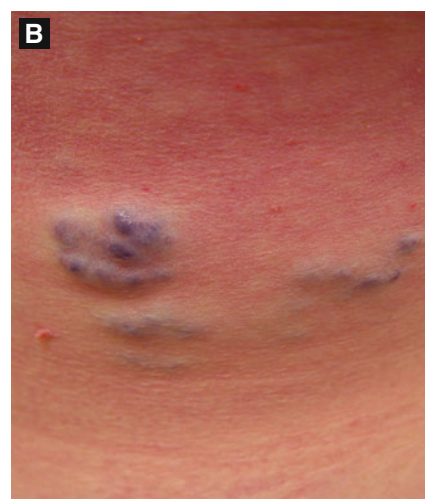
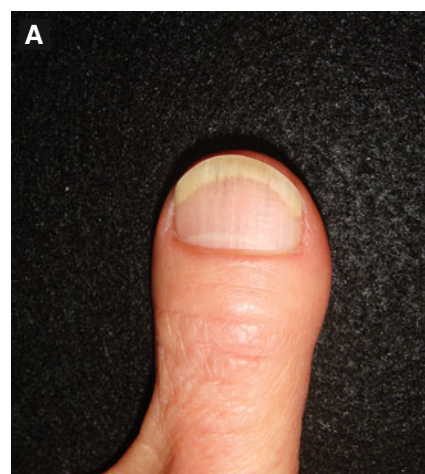
- Sporadic, CREB binding protein
- Vascular malformation, broad thumbs, beaked nose, mental retardation, congenital heart defects, cryptorchidism

Rubinstein Taybi – Roomy (broad) Thumbs

### Mafucci Syndrome

- Sporadic, PTH/PTHrP type I receptor
- Venous malformations (superficial/deep) of hands/feet, benign enchondromas (benign cartilaginous tumor), ↑ risk of chondrosarcomas within enchondromas and other less common sarcomas; angiosarcomas usually fatal

MafuCCI – Cartilaginous tumor (enchondroma), Chondrosarcoma



**Figure 2.28**  
**A: Rubinstein–Taybi syndrome**  
**B: Blue rubber bleb syndrome**  
 (Courtesy of Dr. Michelle B. Bain)  
**C: Cornelia de Lange syndrome**  
 (Courtesy of Dr. Karen Bryson)



**Blue Rubber Bleb Nevus Syndrome (Bean Syndrome) (Figure 2.28B)**

- Sporadic (sometimes AD), TIE2 gene mutation (tyrosine kinase activating mutation)
- Multiple tender cutaneous and GI venous malformations
- Presents with compressible, blue papulonodules on trunk/arms, painful with ↑ lesional hyperhidrosis, + nocturnal pain characteristic, GI malformations can cause GI bleeding, intussusception

**Cornelia de Lange Syndrome (Figure 2.28C)**

- AD, but mainly sporadic, NIPBL (nipped-beta-like gene)
- Cutis marmorata, synophrys, trichomegaly, craniofacial abnormalities, MR, deafness, low-pitched cry, clinodactyly

**Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu) (Figure 2.29A, B)**

- AD, HHT1 (endoglin), and HHT2 (ALK1) gene mutation
- Multiple mucocutaneous and GI telangiectasias: epistaxis, telangiectasis (skin/mucosa), GI bleeding, pulmonary arteriovenous malformations

**Hereditary Lymphedema (Milroy Disease)**

- AD, FLT4 gene mutation, encodes VEGF receptor-3 (tyrosine kinase R in lymphatic vessels)
- Congenital lymphedema, chylous ascites, ± cystic hygroma

**Lymphedema–Distichiasis Syndrome**

- AD, FOXC2 mutation, encodes transcription factor
- Late-onset lymphedema, double row of eyelashes (distichiasis), ± trichiasis

**Noonan Syndrome**

- AD, PTPN11 gene, encodes protein tyrosine phosphatase SHP2
- Webbed neck (mimics Turner syndrome), characteristic facies (hypertelorism), undescended testicles, low posterior neck hairline, pulmonary stenosis, lymphedema, keloid formation, KP atrophicans (ulerythema of the eyebrows)

**Turner Syndrome**

- XO genotype
- Webbed neck, low posterior hairline, congenital lymphedema, abnormal sexual development, primary amenorrhea, aortic coarctation

**Meige Lymphedema (Hereditary Lymphedema II)**

- Late-onset lymphedema (around puberty)

**H. DERMAL DISORDERS****Osteogenesis Imperfecta (OI)**

- AD/AR, mutation in type I collagen gene ( $\alpha 1$  and  $\alpha 2$  chains)
- Decreased elasticity, easy bruising, hearing loss secondary to otosclerosis, mitral valve prolapse
- Type I: fractures, bowing, kyphoscoliosis
- Type II (severe): beaded ribs, crumpled humeri, abducted thighs

**Ehlers–Danlos Syndrome (Figure 2.29C, Table 2-5)****Figure 2.29****A:** HHT (Courtesy of Dr. Paul Getz)**B:** HHT (Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatological Diseases*. New York, NY: Springer; 2007)**C:** Molluscoid tumors in EDS(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

**Table 2-5 Classification of Ehlers–Danlos Syndrome (EDS)**

EDS Type	Traditional Classification	Inh	Gene Defect	Clinical Findings
<b>Classic</b>	I (Gravis)	AD	COL5A1 or COL5A2 ( <b>Type V collagen</b> )	Hyperextensible skin, joint laxity, skin fragility with fish-mouth scars and cigarette paper texture, + Gorlin sign (touch tip of nose with tongue), <b>absence of frenulum</b> (inferior labial or lingual), molluscoid pseudotumors (spongy tumors over scars/pressure points), ± mitral valve prolapse, ± premature rupture of membranes in labor (type I)
	II (Mitis)	(AR)	(Tenascin X deficiency)	
<b>Hypermobility</b>	III (Benign hypermobile)	AD	TNXB ( <b>Tenascin X</b> in 10%)	Striking joint hyperextensibility (subluxations/dislocations), <b>minimal skin involvement</b> , degenerative joint disease
<b>Vascular</b>	IV (Arterial-ecchymotic)	AD	COL3A1 ( <b>Type III collagen</b> )	Thin translucent skin, <b>visible veins</b> under skin, <b>vascular fragility</b> (arterial, GI, uterine rupture), extensive <b>bruising</b> , hypermobility of small joints (hands/feet)
<b>Kyphoscoliosis</b>	VI	AR	PLOD ( <b>Lysyl hydroxylase</b> )	Kyphoscoliosis, respiratory problems, muscle weakness, joint laxity, <b>ocular fragility</b> (glaucoma, retinal detachment)
<b>Arthrochalasia</b>	VIIA, VIIB	AD	COL1A1 or COL1A2 ( <b>Type I collagen</b> )	<b>Marked joint hypermobility</b> with moderate cutaneous elasticity, <b>dislocation of large joints (bilateral congenital hip dislocations)</b> , scoliosis, easy bruising
<b>Dermatosparaxis</b>	VIIC	AR	ADAMTS2 ( <b>Procollagen N-proteinase</b> )	Extremely <b>fragile and sagging skin</b> , easy bruising, hernias
<b>Other</b>	V, VIII, X	Of note, type IX reclassified as occipital horn syndrome, allelic with Menkes disease (ATP7A, lysyl oxidase defect)		
		Type XI reclassified as familial joint hypermobility syndrome (new type X)		
	V	XLR		Hyperextensible skin, orthopedic abnormalities, bruising
	VIII	AD	?	<b>Periodontitis</b> + EDS I/II findings
	X		Fibronectin deficiency	Bruising, joint hypermobility
	EDS, cardiac valvular	AR	Collagen I ( $\alpha 2$ chain)	Heart valve defects + EDS I findings
	EDS, progeroid	AR	B4GALT7 ( <b>Galactosyl transferase 1</b> )	Progeroid facies, osteopenia, MR, growth retardation, skin hyperextensibility, joint hypermobility

**Marfan Syndrome**

- AD, fibrillin 1 and 2 defect
- Tall stature, ectopia lentis (upward dislocation), myopia, arachnodactyly, long limbs, aortic dilation with rupture, mitral valve prolapse (MVP), striae, elastosis perforans serpiginosa (EPS); death from cardiac complications

**Pseudoxanthoma Elasticum (PXE)** (Figure 2.30A)

- AR (most common) or AD, ABCC6 gene mutation (transmembrane transporter gene)
- Fragmented/calcified elastin of skin/eyes/arteries, “plucked chicken” skin on flexures, angioid streaks (rupture in Bruch’s membrane) with retinal hemorrhage, gastric artery hemorrhage, MVP, hypertension, myocardial infarction

**Cutis Laxa**

- AR, FBLN5 gene, fibulin 5, AD (elastin gene and FBLN5), XLR (ATP7A gene)
- Presents with loose, pendulous skin (inelastic), arterial rupture, lung abnormalities, visceral diverticulae/hernia, joint dislocation, pulmonary emphysema (AR inheritance), newborn with hypoplastic lungs
- Acquired form: Marshall syndrome

**Congenital Contractural Arachnodactyly**

- AD, fibrillin 2, crumpled ears, long limbs, arachnodactyly

**Focal Dermal Hypoplasia (Goltz Syndrome)** (Figure 2.30B, C)

- XLD, lethal in males
- Presents with linear atrophy following Blaschko’s lines following areas of fat herniation, osteopathia striata, colobomas, oral papillomas, lobster claw deformity of hands, syndactyly, alopecia, notched nasal ala

Goltz – think of a lobster using its claw along the sand causing linear striations (osteopathia striata)

**Berardinelli–Seip Congenital Lipodystrophy**

- BSCL2 gene mutation (nuclear lamins)
- Generalized lipodystrophy, hyperlipemia, acanthosis nigricans, insulin-resistant DM, hepatomegaly

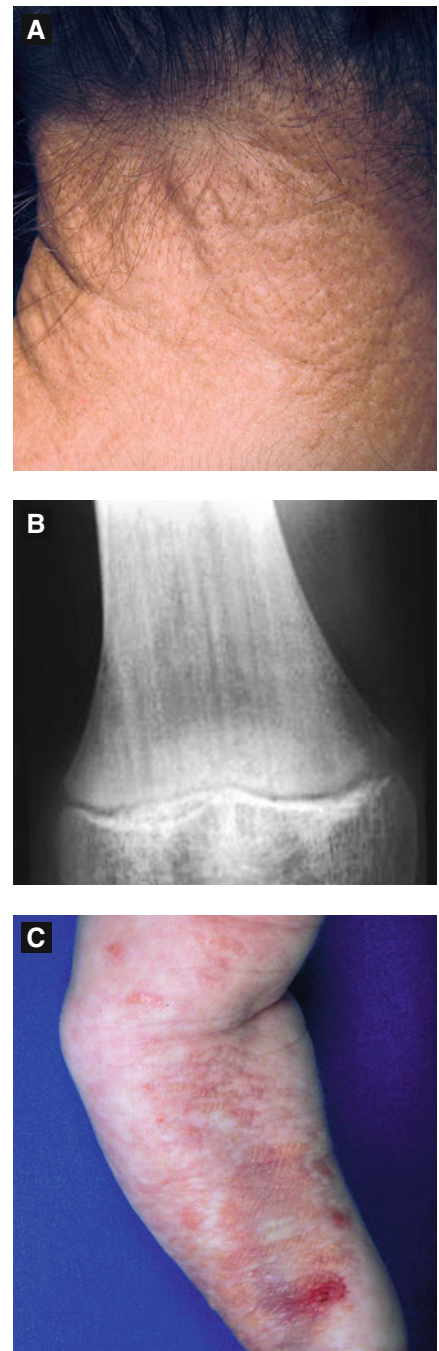
**Familial Partial Lipodystrophy**

- AD, LMNA gene mutation (lamin A/C)
- Symmetric lipoatrophy of trunk/limbs, tuberoeruptive xanthomas, acanthosis nigricans, hypertriglyceridemia

**Buschke–Ollendorf Syndrome** (Figure 2.31A, B)

- AD, LEMD3 (MAN1) gene mutation, encodes inner nuclear membrane protein
- Elastomas (dermatofibrosis lenticularis disseminata) presenting as yellow papules involving trunk, buttocks, arms, and osteopoikilosis (ectopic calcifications in bone), not prone to fracture

**BUSH**ke – think of small **bush**-like opaque areas within the bone (osteopoikilosis)

**Figure 2.30**

**A: Pseudoxanthoma elasticum**  
(Courtesy of Dr. Sophie M. Worobec)

**B: Osteopathia striata**  
(Reprint from Offiah AC, Hall CM. Radiological diagnosis of constitutional disorders of bone. *Pediatric Radiology*. 2003; 33(3): 153–61)

**C: Focal dermal hypoplasia**  
(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)



**Lipoid Proteinosis (Urbache–Wiethe Disease)**

- AR, ECM1 gene mutation (extracellular matrix protein 1)
- “String of pearls” over eyelids, hoarse voice, bean-shaped temporal/hippocampal calcification (with occasional seizures), large wooden tongue, waxy yellow papules of face/oropharynx

**Beare-Stevenson Cutis Gyrata Syndrome (Figure 2.31C)**

- FGFR2 gene mutation (fibroblast growth factor receptor 2)
- Cutis gyrata, acanthosis nigricans, anogenital anomalies, craniosynostosis, furrowed palms/soles

**I. DISEASES OF THE HAIR AND NAILS****Menkes Disease**

- XLR, ATP7A mutation, encodes ATP-dependent copper transporter
- ↓ Serum copper levels, pili torti (most common), trichorrhexis nodosa, short brittle “steel wool” hair, sparse eyelashes/eyebrows, cupid’s bow upper lip, progressive CNS deterioration, seizures, tortuous arteries

**Monilethrix**

- AD, human hair keratin hHb1 and hHb6
- Beaded hair with elliptical nodes along hair shaft, keratosis pilaris

MoneliThRIX – think of **trix** cereal and each piece as an elliptical node causing a beaded appearance

**Trichorhinophalangeal Syndrome**

- AR/AD, TRPS1 gene
- Sparse hair, pear-shaped nose, cone-shaped epiphyses

TrichoRhinoPhalangeal (**TRP**) –think of **TRiP**ping so many times that your nose becomes pear-shaped

**Uncombable Hair Syndrome (Figure 2.32A)**

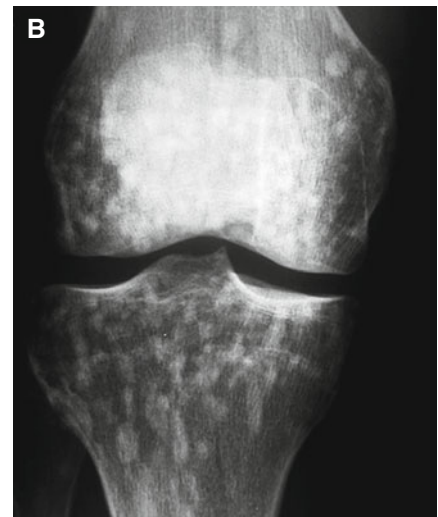
- AD, AR or sporadic
- Pili trianguli et canaliculi (triangular cross-sectional appearance, longitudinal groove), blonde “spun glass” hair
- Possible improvement with biotin

**Tricho-dento-osseous Syndrome**

- AD, DLX3 homeobox gene, curly/kinky hair at birth (may straighten after puberty), dental pits, ↑ bone density

**Björnstad Syndrome**

- AR, pili torti, deafness, normal intelligence and lifespan

**Figure 2.31****A: Elastomas**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009)

**B: Osteopoikilosis**

(Reprint from Dheedene A. The heterozygous *Lem3+/GT* mouse is not murine model for osteopoikilosis. *Calcified Tissue Int.* 2009; 85 (6): 546–51)

**C: Cutis verticis gyrata**

(Courtesy of Dr. Michelle B. Bain)

**Papular Atrichia**

- AR, human homolog of mouse hairless gene mutation
- Loss of natal hair with subsequent generalized atrichia

**Nail–Patella Syndrome (Figure 2.32B)**

- AD, LMX1B mutation
- Triangular lunulae, absent/hypoplastic patella, posterior iliac horns, thickened scapulae, glomerulonephritis, Lester iris (hyperpigmented papillary margin of iris), radial head subluxation

**PATELLa** – Posterior iliac horns, Absent patella, Thickened scapula, Eye (lester iris), Lunulae (triangular), gLomerulonephritis

**Pachyonychia Congenita**

- Mainly AD, K6a/16 mutation (type I), K6b/17 (type II)

<b>Jadassohn–Lewandowsky</b> (Type I)	Dystrophic nails, palmoplantar keratoderma (PPK), oral leukokeratosis (benign)
<b>Jackson–Lawler</b> (Type II)	Dystrophic nails, PPK, steatocystomas, epidermal cysts, natal teeth

**J. DISORDERS OF CORNIFICATION****Ichthyosis Vulgaris (IV) (Figure 2.32C)**

- AD, decreased/absent profilaggin (keratohyalin granules)
- Presents few months after birth to early childhood with fine, white scales on extensor surfaces; flexures spared, hyperlinear palms/soles, atopic diathesis
- Histology: attenuated/absent granular layer, retention hyperkeratosis
- Acquired form of IV associated with internal disease, malignancies, and some medications

**Figure 2.32****A: Uncombable hair syndrome**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

**B: Triangular lunulae (NPS)**

(Reprint from Tosti A, Ralph DC, Piraccini BM, Iorizzo M. *Color Atlas of Nails*. Heidelberg: Springer; 2010)

**C: Ichthyosis vulgaris**

(Courtesy of Dr. Paul Getz)

**X-linked Ichthyosis (XLI)**

- XLR, defect in steroid sulfatase (STS, arylsulfatase C)
- Presents around infancy with mild erythroderma and large translucent scales → evolves into adherent brown “dirty” scales over extremities, trunk, neck; variable involvement of flexures, sparing of palms/soles/face
- Mother (with affected fetus): low/absent estrogen in urine/amniotic fluid → labor fails to progress
- Other associations: comma-shaped corneal opacities, cryptorchidism (↑ risk of testicular CA)
- Histology: hyperkeratosis or parakeratosis overlying normal or slightly thickened granular layer
- Tests: serum lipoprotein electrophoresis (detects accumulation of cholesterol sulfate)

**Lamellar Ichthyosis (Nonbullous Congenital Ichthyosiform Erythroderma, Nonbullous CIE) (Figure 2.33A–C)**

- AR, mutation in TGM1 gene (transglutaminase deficiency) or ABCA12 mutation (ATP binding cassette A12)
- Presents at birth with collodion membrane with underlying erythroderma → evolves to thick, dark scales with prominent flexural involvement; no improvement with age
- Associated ectropion, eclabium, scarring alopecia
- PPK, heat intolerance (heat stroke), hypernatremia
- Histology: massive orthokeratotic hyperkeratosis, acanthosis

**Congenital Ichthyosiform Erythroderma (Nonbullous CIE)**

- AR (some AD), TGM1 gene, few ALOXE3 or ALOX12B gene mutation (encode lipoxygenase 3 and 12R-lipoxygenase, respectively)
- Presents at birth with collodion membrane → generalized erythroderma and persistent scaling, flexures involved, PPK; no improvement with age
- Associated scarring alopecia, ectropion, nail dystrophy (similar to LI but milder), heat intolerance

**Ichthyosis Bullosa of Siemens**

- AD, keratin 2e (K2) gene defect
- Presents at birth with mild erythroderma and mild blistering → evolves into brown hyperkeratotic plaques over joints, flexures, dorsal hands and feet; spares palms/soles

**Figure 2.33****A: Lamellar ichthyosis\*****B: Lamellar ichthyosis\*****C: Lamellar ichthyosis\***

\* Courtesy of Dr. Paul Getz



**Epidermolytic Hyperkeratosis (EHK or Bullous CIE) (Figure 2.34A–C)**

- AD, keratin 1 and keratin 10 gene mutations
- Presents at birth with initial erythroderma, bullae, denuded skin → evolves into verrucous hyperkeratotic plaques, flexural involvement, PPK
- Histology: massive orthokeratotic hyperkeratosis, hypergranulosis, cytolysis of suprabasal/granular layers, clumped tonofilaments (keratin intermediate filaments)
- Failure to thrive, hypernatremic dehydration, recurrent infections (bronchopneumonia, sepsis)

**Harlequin Ichthyosis**

- AR, ABCA12 mutation (ATP binding cassette A12)
- Presents at birth with encasement of hard, thickened restrictive stratum corneum with severe ectropion, eclabium, mitten-like hands and feet
- Death within few days of birth due to respiratory difficulties and sepsis
- Oral retinoid may prolong survival

**Netherton Syndrome (Figure 2.35A)**

- AR, SPINK5 gene defect (encodes serine protease inhibitor LEKT1)
- Presents at or near birth with generalized erythroderma and scaling, ± collodion membrane
- Triad of congenital ichthyosis (ichthyosis linearis circumflexa {ILC} or congenital ichthyosiform erythroderma {CIE}), trichorrhexis invaginata (TI, bamboo-like or ball-and-socket appearance of hair shaft), and atopy
- ILC: serpiginous or circinate erythematous plaques with double-edged scale
- TI: most specific hair finding (eyebrow with high yield), trichorrhexis nodosa is most common

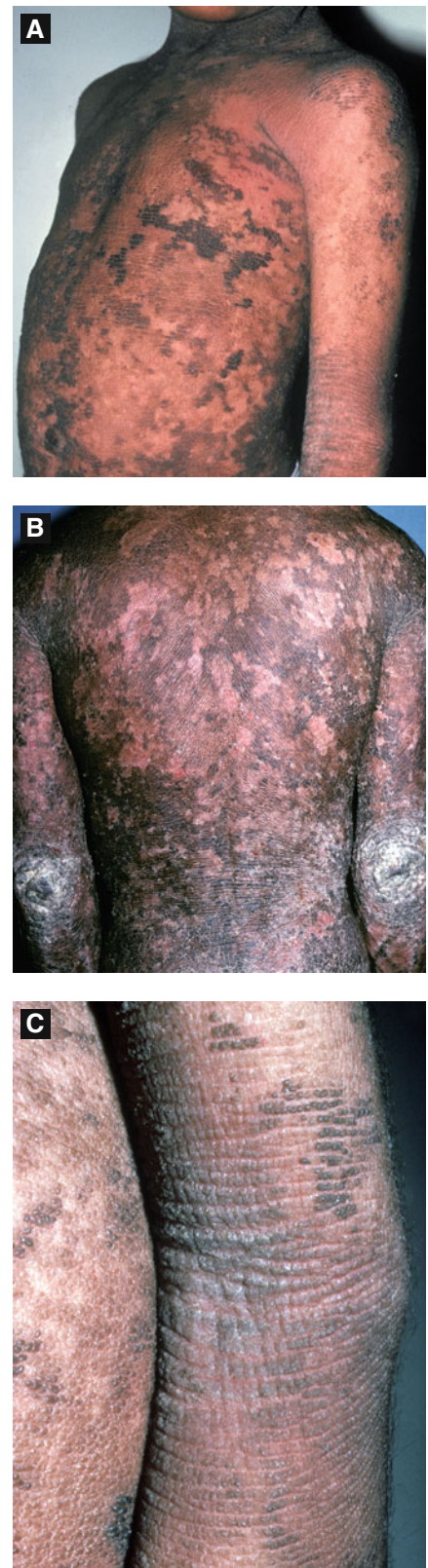
**Sjögren–Larsson Syndrome**

- AR, FALDH gene defect (encoding fatty aldehyde dehydrogenase) → involved in synthesis of epidermal lipids and catabolism of sphingolipids in the brain
- Presents at or near birth with erythema, generalized ichthyosis and pruritus → evolves into dark scales on lower abdomen, flexures, and neck with persistent pruritus, palmoplantar keratoderma (PPK)
- Ichthyosis, spastic ditetraplegia (scissor gait), MR, perifoveal “glistening white dots” in ocular fundus

**SJO** Gren – **Show**y Glistening white dots  
**sJOG**ren – think of trying to **JOG** with a spastic gait

**CHILD Syndrome (Figure 2.35B)**

- Congenital **hemidysplasia** with ichthyosiform erythroderma and **limb defects**
- XLD, NSDHL gene defect, encodes NADPH steroid dehydrogenase-like protein (enzyme 3 $\beta$ -hydroxysteroid-dehydrogenase)
- Presents at or near birth with striking unilateral ichthyotic erythroderma (face typically spared); over time erythema fades while hyperkeratosis persists
- Ipsilateral alopecia, ipsilateral organ aplasia/agenesis, ± cleft palate
- Ipsilateral skeletal defects such as hypoplasia of digits or ribs to complete amelia, stippled epiphyses (seen in early infancy and resolves during childhood)

**Figure 2.34****A: EHK\*****B: EHK\*****C: EHK\***

\* Courtesy of Dr. Paul Getz

### Conradi–Hünemann–Happle Syndrome (XLD Chondrodysplasia Punctata) (Figure 2.35C)

- XLD (different from severe AR rhizomelic form), mutation in EBP gene, coding emopamil-binding protein (sterol isomerase activity) → accumulation of 8(9) cholesterol and 8-dehydrocholesterol (impaired cholesterol synthesis)
- Presents at birth with ichthyosiform erythroderma → hyperkeratosis replaced by linear/patchy follicular atrophoderma and ice pick–like scars
- Chondrodysplasia punctata: stippled or punctate calcification of the epiphyses or “stippled epiphyses” (detected during infancy)
- Cataracts, deafness, scarring alopecia, frontal bossing with flat nasal bridge

CONradi – think of a CON man who becomes crippled with **stippled** epiphyses

### Chondrodysplasia Punctata (distinct from XLD CP)

- XR, arylsulfatase E defect, also can be AD

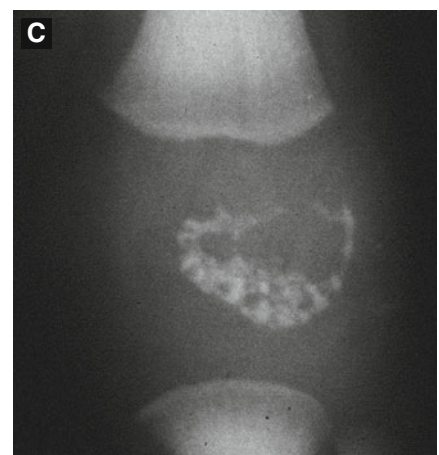
### Rhizomelic Chondrodysplasia Punctata

- AR, PEX7 gene defect (peroxisomal biogenesis disorder)
- Presents with diffuse fine scaling and erythema; alopecia
- Punctate chondrodysplasia, cleft vertebrate, respiratory compromise

### KID Syndrome (Keratitis–Ichthyosis–Deafness Syndrome)

- AD (few AR), GJB2 gene defect (encoding connexin 26)
- Presents at or near birth with symmetric erythematous hyperkeratotic plaques on knees, elbows, and face; PPK with grainy or stippled appearance
- Congenital sensorineural deafness, vascularizing keratitis with secondary blindness, photophobia, abnormalities of teeth/nails, ↑ infections, ↑ risk (rare) of SCC

KID Syndrome – **K**onnexin 26



**Figure 2.35**

**A: ILC in Netherton syndrome**  
(Courtesy of Dr. Michelle B. Bain)

**B: CHILD syndrome**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

**C: Chondrodysplasia punctata**

(Reprint from Laxer RM, ed. *The Hospital for Sick Children: Atlas of Pediatrics*. Philadelphia, PA: Current Medicine; 2005)



**Refsum Disease (Figure 2.36A)**

- AR, mutation of PAHX (PHYH) gene (peroxisomal phytanoyl-CoA hydroxylase) or PEX7 gene (biogenesis factor 7) → excessive accumulation of phytanic acid
- Presents at childhood/adolescence with variable symptoms but typically mild ichthyosis (like ichthyosis vulgaris), cerebellar ataxia, peripheral neuropathy, “salt and pepper” retinitis pigmentosa, deafness
- **Infantile Refsum** (onset at birth): mutation in PEX1, PEX2, or PEX26
- Treat with dietary restriction of phytanic acid

**Ref SUM** – REtinis pigmentosa, SOME salt and pepper please

**Darier Disease (Keratosis Follicularis) (Figure 2.36B, C)**

- AD, ATP2A2 gene mutation, encodes SERCA2 (sarcoendoplasmic reticulum calcium ATPase)
- Presents with hyperkeratotic papules coalescing into warty plaques in a seborrheic distribution
- Acrokeratosis verruciformis of Hopf: verrucous papules on dorsum of hands
- Palmar keratosis/pits
- Nails: red and white alternating longitudinal bands, V-shaped nicks at distal nail plate, subungual hyperkeratosis
- Oral: cobblestoning of oral and anogenital mucosa
- Histology: acantholysis with corp ronds and grains

dArier – 2A2

**K. OTHER CONDITIONS**

Palmoplantar Keratodermas (see Tables 2-6, 2-7)

Ectodermal Dysplasias (see Table 2-8)

Metabolic and Enzyme Deficiency Diseases (Table 2-9)

Signs of Spinal Dysraphism (Table 2-10)

Keratinopathies (Table 2-11)



**Figure 2.36**

**A: Retinitis pigmentosa**

(Reprint from Hoffman GF, Zschocke J, Nyhan WL. *Inherited Metabolic Diseases*. Berlin: Springer; 2010)

**B: Darier disease**

(Courtesy of Dr. Paul Getz)

**C: Darier disease**

(Courtesy of Dr. Paul Getz)

Table 2-6 Diffuse Palmoplantar Keratodermas

Disease	Type	Inh	Mutation	Clinical Appearance
<b>Non-epidermolytic PPK</b> (Unna-Thost Syndrome)	Diffuse	AD	K1	PPK with erythematous border, hyperhidrosis, secondary tinea infections, pitted keratolysis, no transgrediens
<b>Epidermolytic PPK</b> (Vörner Syndrome)	Epidermolytic	AD	K1 or K9 (most common)	Clinically similar to non-epidermolytic PPK but histology shows epidermolytic hyperkeratosis
<b>Mal de Meleda</b>	<b>Transgredient</b>	AR	<b>SLURP-1</b> gene (encodes protein: Secreted Ly-6/uPar related protein)	Transgredient PPK (hands, feet, elbows, knees), hyperhidrosis with malodor and secondary infections, <b>perioral erythema</b> , thickened nails
<b>Vohwinkel Syndrome, Classic</b> (Keratoderma Hereditaria Mutilans)	<b>Mutilating keratoderma + deafness</b>	AD	<b>GJB2</b> (encodes connexin 26)	Diffuse honeycomb-like PPK, <b>pseudoainhum</b> , <b>starfish-shaped</b> keratoses of joints, sensorineural <b>deafness</b> , linear keratotic plaques of knees, scarring alopecia
<b>Vohwinkel Syndrome, Variant</b>	Mutilating + ichthyosis	AD	<b>Loricrin</b> (cornified envelope protein)	Similar to classic Vohwinkel, but no deafness and more generalized ichthyosis
<b>Papillon-Lefèvre Syndrome</b>	PPK + periodontitis	AR	<b>Cathepsin C</b> (lysosomal protease)	<b>Periodontitis</b> , early loss of teeth, transgredient erythematous PPK with psoriasiform lesions on extremities, <b>calcification of falx/tentorium</b> , hyperhidrosis
<b>Haim-Munk Syndrome</b>	PPK + periodontitis + onychogryphosis	AR	Cathepsin C	Papillon-Lefevre syndrome + <b>onychogryphosis</b> , arachnodactyly, acroosteolysis
<b>Naxos Disease</b>	PPK + woolly hair + cardiomyopathy	AR	<b>Plakoglobin</b>	<b>Woolly hair</b> , <b>right ventricular cardiomyopathy</b> with arrhythmias, PPK
<b>Carvajal Syndrome</b>	PPK + woolly hair + cardiomyopathy	AR	Desmoplakin	<b>Dilated cardiomyopathy</b> , PPK in first year of life, <b>woolly hair</b>
<b>Olmsted Syndrome</b>	Mutilating PPK + periorificial plaques	?	? (possible K5 and K14)	PPK (initially focal, then widespread) leading to flexion deformities, autoamputation, erythematous hyperkeratotic <b>perioral plaques</b>
<b>Non-epidermolytic PPK with deafness</b>	PPK + sensorineural deafness	?	Connexin 26 or A7445G (mitochondrial)	PPK, progressive sensorineural deafness

**Table 2-7 Focal Palmoplantar Keratodermas**

Disease	Inh	Mutation	Clinical Appearance
<b>Howel–Evans Syndrome</b>	AD	TOC gene (tylosis-oesophageal carcinoma)	Focal PPK over <b>pressure areas</b> (balls of feet > hands), oral leukokeratosis, ↑ <b>esophageal CA</b>
<b>Richner–Hanhart Syndrome</b> (Tyrosinemia Type II)	AR	Hepatic tyrosine amino-transferase (TAT)	Pseudoherpetic <b>keratitis</b> , dendritic corneal ulcers (tyrosine crystal deposition in eyes), <b>painful focal PPK</b> , progressive MR, treat with <b>diet restricted</b> in tyrosine and phenylalanine
<b>Punctate PPK</b> (Keratosis Punctata Palmaris Et Plantaris)	AD	?	Begins during or near adolescence, punctate keratoses on palms, can also occur in palmar creases of patients of African origin
<b>Acrokeratoelastoidosis</b>	AD		Skin-colored papules involving hands and feet
<b>Striate PPK</b>	AD	Desmoglein 1 and desmoplakin 1	Onset in teens/early adulthood, hyperkeratotic linear plaques on volar fingers, diffuse/focal plaques on proximal palms/soles
<b>Erythrokeratoderma Variabilis</b> (Mendes da Costa)	AD	<b>GJB3, GJB4</b> (connexin 30.3 and 31)	Erythematous migratory patches (may last minutes to days), fixed hyperkeratotic plaques, 50% with PPK, flexures spared
<b>Progressive Symmetric Erythrokeratoderma</b>	AD	Likely loricrin mutation or connexin 31	Fixed hyperkeratotic erythematous plaques over joints/extremities, 50% with PPK

**Table 2-8 Ectodermal Dysplasias**

Disease	Inh	Mutation	Clinical Appearance
<b>Hidrotic Ectodermal Dysplasia</b> (Clouston Syndrome)	AD	<b>GJB6</b> (connexin 30)	Hypotrichosis, diffuse PPK, <b>nail dystrophy</b> , <b>NORMAL teeth and sweating</b> , MR, ocular abnormalities
<b>Hypohidrotic (Anhidrotic) Ectodermal Dysplasia</b> (Christ-Siemens-Touraine)	XR	<b>EDA</b> (ectodysplasin A)	Hypotrichosis, <b>periorbital hyperpigmentation</b> , <b>ABSENT or conical teeth</b> , <b>sweating</b> with heat intolerance, <b>NORMAL</b> nails, saddle nose, everted thick lips, ↑ bronchopulmonary infections
	AD, AR	EDAR gene (ED-A receptor)	
<b>Ankyloblepharon-Ectodermal Dysplasia-Clefting Syndrome</b> (AEC) (Hay-Wells)	AD	p63	Chronic <b>erosive scalp dermatitis</b> , abnormal granulation tissue, recurrent bacterial infections, ankyloblepharon, hypotrichosis, 80% cleft lip/palate
<b>Ectodermal Dysplasia-Ectrodactyly-Clefting Syndrome</b> (EEC) (Split Hand-Split Foot-Ectodermal Dysplasia-Clefting)	AD	p63	Ectrodactyly (split hand/foot), hearing loss, nail dystrophy, ± PPK, 70% cleft lip/palate, sparse and dry hair, hypodontia
<b>Rapp-Hodgkin Syndrome</b>	AD		Mid facial hypoplasia, cleft lip/palate, scalp dermatitis, ↓ sweating, nail dystrophy, hypodontia
<b>Ectodermal Dysplasia/Skin Fragility Syndrome</b>	AR	Plakophilin-1	Trauma-induced bullae (most prominent during infancy), sparse hair, thick dystrophic nails





**Figure 2.37**

**A: Anhidrotic ectodermal dysplasia**  
(Courtesy of Dr. Michelle B. Bain)

**B: Anhidrotic ectodermal dysplasia**  
(Courtesy of Dr. Michelle B. Bain)

**C: Pseudoainhum in Vohwinkel syndrome**  
(Courtesy of Dr. Paul Getz)

**D: Palmoplantar keratoderma in Vohwinkel syndrome**  
(Courtesy of Dr. Paul Getz)

**Table 2-9 Metabolic and Enzyme Deficiency Diseases**

Disease	Inh	Defect	Clinical Findings
<b>Alkaptonuria</b>	AR	Homogentisic acid (HA) oxidase	Blue-gray pigmentation of cartilage (helices), sclera and skin (axilla); urine darkens on standing, arthritis
<b>Biotinidase Deficiency</b>	AR		Alopecia, periorificial dermatitis, developmental delay, seizures; treat with biotin
<b>Fabry Disease</b>	XLR	$\alpha$ -Galactosidase A	Glycosphingolipids in vascular endothelium: multiple angiokeratomas, extremity <b>pain/paresthesias</b> , <b>whorl-like corneal and lenticular opacities</b> , birefringent lipid globules in urine (“ <b>maltese crosses</b> ”), MI, cerebrovascular accident (CVA)
<b>Fucosidosis</b>	AR	$\alpha$ -Fucosidase	Multiple angiokeratomas, coarse facies, growth retardation, dysostosis multiplex, mental retardation
<b>Gaucher Disease</b>	AR	$\alpha$ -Glucosidase (Glucocerebrosidase)	<b>Type I (adult)</b> : no CNS findings + diffuse brown skin pigmentation, thrombocytopenia, hepatosplenomegaly (HSM), bone pain, <b>ehrlenmeyer flask deformity</b> of femoral midshaft
			<b>Type 2 (infant)</b> : no skin findings, severe, rapid death
			<b>Type 3 (juvenile)</b> : chronic neuropathy
<b>Hartnup Disease</b>	AR	SLC6A19	↓ Renal reabsorption of neutral amino acids, pellagra-like dermatosis with photosensitivity, ataxia, tremors
<b>Holocarboxylase Synthetase Deficiency</b>	AR		Alopecia, perioral/perianal dermatitis, metabolic encephalopathy, metabolic acidosis; treat with biotin
<b>Hunter Disease</b>	XLR	Iduronidate sulfatase	Firm, flesh-colored to white papules coalescing over scapula
<b>Hurler Disease</b>	AR	$\alpha$ -L-iduronidase	Mental retardation (MR), HSM, hernia, opacities, gargoyle-like features
<b>Lesch–Nyhan Syndrome</b>	XLR	HGPRT deficiency	Self-mutilation, orange crystals in the diaper, gout, choreoathetosis, MR
<b>Lipoid Proteinosis</b>	AR	ECM1 defect	Pearly papules, hippocampal calcification, infiltration of deposits on lips and tongue (wooden), hoarseness
<b>Neimann–Pick Disease</b>	AR	Sphingomyelinase deficiency (SMPD1)	<b>Type A</b> : failure to thrive, HSM, neurologic deterioration
			<b>Type B</b> : minimal neurologic disease, xanthomas, histiocytic infiltration in viscera, psychomotor delay, muscle weakness, blindness (cherry red spots)
<b>Phenylketonuria</b>	AR	SLC39A4 (zinc transporter)	Diffuse hypopigmentation, eczema, MR, sclero-dermoid changes, blonde hair, blue eyes, urine and skin with mousy odor
<b>Prolidase Deficiency</b>	AR	Prolidase	Skin fragility, ulceration and scarring over lower extremities, photosensitivity, MR, recurrent infections
<b>Wilson’s Disease</b>	AR	ATP 7B (ATPase copper transporting enzyme)	Copper accumulation in liver/brain/cornea, cirrhosis, blue lunula, Kayser–Fleischer rings, ataxia, dementia, hepatomegaly



**Table 2-10 Signs of Spinal Dysraphism (High Risk for Dysraphism if  $\geq 2$  of the Following)**

Hypertrichosis	Dimpling	Skin tags
Tails/pseudotails	Lipomas	Aplasia cutis
Hemangiomas	Dermoid cysts/sinuses	Telangiectasia, capillary malformation, nevi (less likely)

**Table 2-11 Keratinopathies**

Type II Keratin	Type I Keratin	Location of Expression	Associated Disease
1	10	Suprabasal keratinocytes	Epidermolytic hyperkeratosis (Bullous CIE) Unna-Thost PPK (K1) Ichthyosis hystrix of Curth-Macklin (K1)
1	9	<b>Palmoplantar</b> , supra-basal keratinocytes	Epidermolytic PPK (Vörner)
2 (2e)	10	Granular and upper spinous layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Meesmann corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	<b>Basal keratinocytes</b>	Epidermolysis bullosa simplex (EBS) Dowling-Degos disease (K5 alone)
6a	16	Outer root sheath	Pachyonychia congenita I (Jadassohn Lewandowsky) Focal PPK
6b	17	<b>Nail bed</b>	Pachyonychia congenita II (Jackson-Lawler) Steatocystoma multiplex
8	18	Simple epithelium	Cryptogenic cirrhosis
K81 and K86		Hair	Monilethrix
	19	Simple epithelium, bulge cells	
6	16		Hyperproliferative keratinocytes

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# 3

# General Dermatology

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### 3.1 ACNE AND RELATED CONDITIONS

#### A. ACNE VULGARIS AND SPECIAL FORMS (Tables 3-1, 3-2)

##### Acne Vulgaris

- Inflammation of the pilosebaceous unit (PSU) causing comedones, papulopustules and nodules
- Four key pathogenic factors
  - **Abnormal follicular keratinization**
    - ↑ Corneocyte cohesiveness and proliferation
  - ***Propionibacterium acnes* (*P. acnes*) in sebum**
    - Gram + anaerobic rod, resident flora in follicle but acne patients with higher concentration
    - Naturally produces porphyrins (coproporphyrin III), which is the target of light-based acne therapy
    - Secretes lipases which cleave lipids in sebum into pro-inflammatory free fatty acids (FFAs), which are both comedogenic and chemotactic
    - Binds/activate toll-like receptor 2 (TLR2)
  - **Inflammation**
    - ↑ IL-1, IL-8, and TNF- $\alpha$  through TLR-2 pathway
  - **Hormonal effect on sebum due to androgens**
    - ↑ Sebum production due to androgen-stimulated sebaceous glands
    - Androgen receptors present on basal layer of sebaceous gland and ORS of hair follicle; respond to most potent androgen, dihydrotestosterone (DHT), and testosterone (latter produced by gonads and can be converted to DHT via 5 $\alpha$ -reductase)
    - Dehydroepiandrosterone sulfate (DHEA-S): weak androgen produced by adrenal glands
- Microscopic precursor lesion: microcomedo
- May present with non-inflammatory comedones (open/closed), inflammatory papules, pustules,  $\pm$  nodules
- Histology: follicular distension often with ruptured PSU and accompanying brisk inflammatory response,  $\pm$  foreign body reaction with multinucleated giant cells
- Treatment:

<b>Topical therapy</b>	Benzoyl peroxide, retinoids (tretinoin, adapalene, tazarotene), azelaic acid, dapsone, clindamycin, sodium sulfacetamide/sulfur and salicylic acid  Topical retinoids: comedolytic and downregulate TLR-2
<b>Other therapies</b>	Oral antibiotic, isotretinoin, oral contraceptive pill; photodynamic therapy or blue light alone  Cannot combine isotretinoin and tetracycline due to risk of <b>pseudotumor cerebri</b>



**Figure 3.1**  
**A:** Acne conglobata  
**B:** Acne excoriée  
**C:** Acne in PCOS

**Table 3-1 Acne Variants**

Type	Clinical Features
<b>Acne fulminans</b>	<ul style="list-style-type: none"> <li>– Severe form of nodulocystic acne in young males (13–16 years old)</li> <li>– Presents with sudden-onset suppurative nodular acne with ulceration, eschars and <b>systemic symptoms</b> (may include myalgias, arthralgias, fever, ↑ ESR, ↑ WBCs, ± sterile osteolytic bone lesions typically over clavicle or sternum)</li> <li>– Treat with <b>low-dose accutane</b> and <b>prednisone</b> or prednisone alone initially, followed by isotretinoin (to prevent flare and formation of granulation tissue)</li> </ul>
<b>Acne conglobata</b> (Figures 3.1A, 3.2A)	<ul style="list-style-type: none"> <li>– Acute-onset nodulocystic acne without systemic manifestations</li> <li>– Part of the follicular occlusion triad (dissecting cellulitis of scalp, pilonidal cyst and hidradenitis suppurativa)</li> </ul>
<b>Acne excoriée</b> (Figure 3.1B)	<ul style="list-style-type: none"> <li>– Mainly seen in young women with emotional or psychological disorders (such as obsessive-compulsive disorder) who repeatedly pick at lesions</li> <li>– Presents as mild acne with several excoriations, crusted erosions and sometimes ulcerations with subsequent scarring</li> <li>– <b>Antidepressants</b> may be warranted</li> </ul>
<b>Acne with underlying endocrinologic abnormality</b> (Figure 3.1C)	<ul style="list-style-type: none"> <li>– If acne with accompanying hirsutism ± irregular menses, check lab work for hormonal abnormality (check LH, FSH, DHEA-S, free and total testosterone)</li> <li>– Source of androgens <ul style="list-style-type: none"> <li><b>Ovarian androgens:</b> testosterone</li> <li><b>Adrenal androgens:</b> DHEA-S, 17-hydroxyprogesterone</li> </ul> </li> <li><b><u>Polycystic ovarian syndrome (PCOS):</u></b> <ul style="list-style-type: none"> <li>– Seen in 5–10% of women of reproductive age</li> <li>– Androgen excess causing hirsutism, irregular menses, ± polycystic ovaries, obesity, insulin resistance, ↑ LH/FSH ratio, ↓ fertility, ↑ testosterone</li> <li>– Acne lesions typically nodular and involve lower ½ of face (especially <b>jawline</b>)</li> <li>– Treatment: oral contraceptive pill (resulting in ↑ SHBG, ↓ free testosterone), spironolactone (off-label, blocks androgen receptor)</li> </ul> </li> <li><b><u>Late congenital adrenal hyperplasia:</u></b> <ul style="list-style-type: none"> <li>– ↑ DHEA-S or 17-hydroxyprogesterone due to partial deficiency of adrenal enzymes (commonly 21-hydroxylase or 11-hydroxylase)</li> </ul> </li> </ul>
<b>Industrial acne</b>	<ul style="list-style-type: none"> <li>– Due to exposure to insoluble cutting oils or chlorinated aromatic hydrocarbons (such as chlorinated dioxins and dibenzofurans)</li> <li>– Chloracne (form of industrial acne): presents with comedones, pustules and cysts over <b>malar cheeks, retroauricular region, and scrotum</b></li> </ul>
<b>Acne mechanica</b>	<ul style="list-style-type: none"> <li>– Due to repeated obstruction of the pilosebaceous unit through friction/pressure</li> </ul>
<b>Neonatal acne</b> (Cephalic neonatal pustulosis)	<ul style="list-style-type: none"> <li>– Begins around 2 weeks of age and often resolves by third month of age</li> <li>– Presents with erythematous small papules on cheeks</li> </ul>
<b>Infantile acne</b>	<ul style="list-style-type: none"> <li>– Typically begins around 3–6 months of age, resolves within 1–2 years</li> </ul>
<b>Drug-induced acne</b> (Acneiform eruption)	<ul style="list-style-type: none"> <li>– Due to corticosteroid, phenytoin, lithium, isoniazid, iodides, <b>epidermal growth factor receptor inhibitors</b> (EGFRI: cetuximab, erlotinib, gefitinib), anabolic steroids</li> <li>– Presents with abrupt-onset monomorphic-appearing papules and pustules; comedones typically not seen</li> </ul>



**Table 3-2 Syndromes Associated with Acne**

Syndrome	Clinical Features
<b>PAPA syndrome</b>	<b>Pyogenic Arthritis (sterile), Pyoderma gangrenosum, Acne</b> – Inherited (AD), <b>CD2 binding protein 1</b> (CD2BP1) mutation; CD2BP1 is a pyrin-interacting protein, which is part of inflammatory pathway associated with familial Mediterranean fever, Muckle-Wells syndrome, and familial cold urticaria – Skin changes typically present near or at puberty
<b>HAIR-AN</b>	<b>HyperAndrogenism, Insulin Resistance, Acanthosis Nigrans</b>
<b>SAPHO</b> (Chronic recurrent multifocal osteomyelitis)	<b>Synovitis, Acne (conglobata), Pustulosis (palmoplantar), Hyperostosis, Osteitis</b> – Inflammatory bone changes (commonly involving <b>sternoclavicular joint</b> , spine {spondyloarthropathy} and long bones); peripheral arthritis also common – 1st line treatment: bisphosphonates suggested in many case reports and series; other treatments include mainstay therapies for psoriatic arthritis (methotrexate, anti-TNF $\alpha$ agents, etc.)

## B. ACNEIFORM CONDITIONS

### Gram-Negative Folliculitis

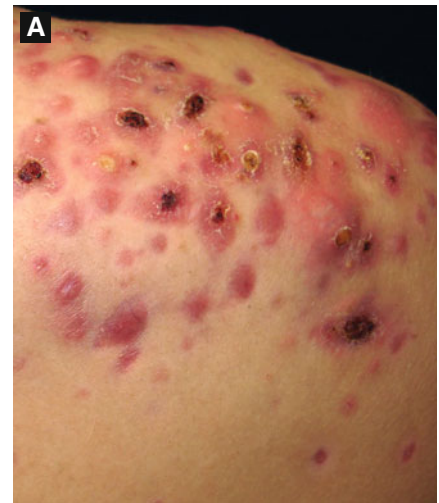
- Exacerbation of acne after long-term antibiotic use
- Presents with centropacial pustules, especially perinasal
- Treat with isotretinoin if severe or recurrent

### Acne Keloidalis Nuchae (Figure 3.2B)

- Chronic folliculitis of occipital scalp and posterior neck in men of African, Hispanic or Asian descent
- Presents initially as inflammatory follicular papules and pustules which over time evolve into firm, dome-shaped papules with fibrosis,  $\pm$  coalesce into keloidal plaques
- Treatment: tretinoin gel, topical and/or systemic antibiotics, punch excision or intralesional corticosteroid injection for papules or keloids

### Pseudofolliculitis Barbae

- Inflammatory condition typically in men of African descent, especially with tightly curled hair
- Distal end of curved hair penetrates epidermis and dermis after being shaved  $\rightarrow$  subsequent foreign-body inflammatory reaction
- Inflammatory papules, pustules and sometimes abscesses in beard region and anterolateral neck; may form hypertrophic scars and keloids
- Treatment: topical or systemic antibiotics, topical corticosteroid, topical clindamycin/benzoyl peroxide; prevention with clippers, chemical depilatories and glycolic acid lotion

**Figure 3.2**

**A:** Acne conglobata, shoulder  
**B:** Acne keloidalis nuchae

**Perioral Dermatitis (Periorificial Dermatitis) (Figure 3.3A)**

- Distinctive dermatitis with discrete papules and pustules with erythematous (sometimes scaly) base around the mouth, nose, and possibly periorbital area
- Previous use of fluorinated topical steroid may cause or exacerbate condition
- Treatment: oral tetracycline, topical metronidazole or azelaic acid

**Acne Inversa (Hidradenitis Suppurativa) (Figure 3.3B)**

- Chronic inflammatory and scarring disease of apocrine gland-bearing skin sites (axillae and anogenital area)
- Initially thought to be due to obstruction of apocrine glands, but now thought to be from occlusion of follicular infundibula with subsequent rupture of the follicle and surrounding inflammation
- Presents with double-ended comedones, tender nodules and sterile abscesses in groin, axillae, perianal and/or inframammary region; sequelae include sinus tracts, chronic drainage, and scarring (hypertrophic scars, rope-like elevation of skin, dermal contractures)
- Histology: follicular hyperkeratosis, rupture of follicular epithelium, heavy inflammatory infiltrate (lymphocytes, neutrophils, plasma cells) around hair follicles  $\pm$  sweat glands (sometimes extending to apocrine glands), abscess formation, foreign body-type granulomas, fibrosis in late stages
- Treatment: weight reduction, antiseptic soap, absorbent powder, topical aluminum chloride, intralesional corticosteroid injection into early inflammatory lesions, systemic corticosteroids (but typically flare when discontinued), isotretinoin (results often disappointing), acitretin, surgical excision and grafting; avoid incision and drainage (can result in scarring and chronic sinus tract formation)

**Fox-Fordyce Disease (Figure 3.3C)**

- Chronic pruritic disorder of the apocrine glands due to obstruction and dilation
- Intensely pruritic, dome-shaped flesh-colored follicular papules in axillae,  $\pm$  anogenital and periareolar skin
- Treatment (difficult): topical and intralesional corticosteroids, topical tretinoin, topical clindamycin

**Figure 3.3****A: Perioral dermatitis****B: Hidradenitis suppurativa****C: Fox-Fordyce disease***(Courtesy of Dr. Sophie M. Worobec)*

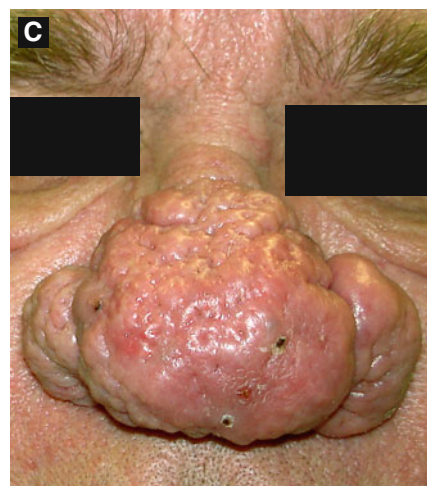
**C. ROSACEA** (Figure 3.4A–C)

- Chronic inflammatory condition of facial pilosebaceous units with increased vascular hyperreactivity; common in fair-skinned patients with peak in the third to fifth decade
- Presents with easy flushing and gradual reddening of complexion; exacerbating factors may include particular foods (especially spicy), alcoholic beverages, UV exposure, hot weather, warm beverages, and exercise

Type	Clinical Findings
<b>Erythematotelangiectatic</b> (Type 1)	Prolonged flushing (>10 min), persistent central facial erythema, ± telangiectasias, ± burning/stinging sensation, easy irritation
<b>Papulopustular</b> (Type 2)	Persistent central facial erythema with acneiform pustules and papules (no comedones)
<b>Phymatous</b> (Type 3)	Indurated erythematous to yellow-brown papules/nodules with persistent edema; almost exclusively in men; rhinophyma (subtype) over distal half of nose; less common sites include forehead, chin, philtrum, ears and eyelids
<b>Ocular</b> (Type 4)	Xerophthalmia, tearing, pain, blurry vision, blepharitis, conjunctivitis, recurrent chalazion, keratitis, iritis, scleritis

Treatment of choice for ocular rosacea: oral antibiotic

- **Steroid rosacea:** use of oral/topical corticosteroid results in exacerbation of disease after initial improvement
- **Granulomatous rosacea:** red-brown papules/nodules with underlying granulomatous inflammation
- Histology: early lesions with dilated blood and lymphatic vessels; later lesions show lymphectasia, perivascular and perifollicular lymphohistiocytic infiltrate, ± poorly organized granulomas, dermal fibrosis, sebaceous gland hyperplasia, ± *Demodex folliculorum* mites within infundibula
- Treatment:
  - Sun protection and avoidance of triggers, green-tinted makeup (conceals redness)
  - Topical therapy: metronidazole or azelaic acid best for inflammatory lesions, sodium sulfacetamide/sulfur
  - Oral therapy: tetracyclines, macrolides, isotretinoin
  - Other: pulsed-dye laser or intense pulsed light



**Figure 3.4**  
**A: Rosacea, papulopustular**  
 (Courtesy of Dr. Paul Getz)  
**B: Rosacea, granulomatous**  
 (Courtesy of Dr. Iris K. Aronson)  
**C: Rhinophyma**



## D. ROSACEA VARIANTS

### Lupus Miliaris Disseminatus Faciei (Figure 3.5A)

- Yellow-brown to red small monomorphic smooth papules on malar cheeks and periorifically
- Lack history of flushing and lack telangiectasias
- Histology: prominent small granulomas,  $\pm$  central necrosis or caseation
- Treatment: long term therapy with minocycline or isotretinoin

### Pyoderma Faciale (Rosacea Fulminans) (Figure 3.5B)

- Mainly seen in postadolescent females; may be rare variant of rosacea
- Presents with acute onset of erythematous papules, pustules, nodules and abscesses in centrafacial region with background of dull cyanotic erythema,  $\pm$  draining sinuses;  $\pm$  mild systemic symptoms (myalgias, fever,  $\uparrow$  ESR,  $\uparrow$  WBC)
- Treatment: initial use of oral corticosteroid followed by low-dose isotretinoin and slow taper of corticosteroid

### Morbihan's Disease (Solid Facial Edema)

- Presents with woody, nonscaling edema involving midline face and cheeks
- Treatment: isotretinoin  $\pm$  ketotifen  $\times$  4–5 months

## 3.2 PAPULOSQUAMOUS, LICHENOID AND ECZEMATOUS DERMATOSES

### A. PAPULOSQUAMOUS DERMATOSES

#### Psoriasis Vulgaris with Subtypes (Figures 3.5C and 3.6A–C)

- Polygenic inflammatory disease with chronic, recurrent course; affects 2% of population
- Bimodal onset with third or sixth decade; earlier onset associated with more severe disease
- Pathogenetic factors
  - **Abnormal T cell activation**
    - New view as  $T_H17$  disease; T cell-mediated autoimmunity toward poorly defined antigens
    - Cytokine profile:
      - $\uparrow$  IL-2, IFN $\gamma$  ( $T_H1$  cytokines)
      - $\uparrow$  IL-1, IL-6, TNF $\alpha$  (innate cytokines)
      - $\uparrow$  IL-12 (stimulates  $T_H1$  cells)
      - $\uparrow$  IL-23 (stimulates  $T_H17$  cells)
      - $\uparrow$  IL-22, IL-17, TNF $\alpha$  ( $T_H17$  cytokines)
      - IL-22 correlates with disease severity
      - T cell disease supported by response to T cell inhibitors like cyclosporine; worsening through IFN $\gamma$

IL-12 and IL-23 have common subunit p40: target of ustekinumab



**Figure 3.5**

**A: Lupus miliaris disseminatus faciei**  
(Courtesy of Dr. Iris K. Aronson)

**B: Pyoderma faciale**  
(Courtesy of Dr. Paul Getz)

**C: Plaque psoriasis**



- **Abnormal keratinocytes**

- ↑ Mitotic activity and leukocyte recruitment; keratinocytes move to upper layer in 3–5 days (vs. normal 28 days)
- ↑ Human  $\beta$ -defensin-2 (hBD2), secretory leukocyte protease inhibitor (SLPI), and skin-derived anti-leukoproteinase (SKALP): antimicrobial peptides resulting in ↓ risk of secondary infection
- ↑ Involucrin in all layers (except basal)
- Shed without loss of nucleus (parakeratotic scales)
- Epidermal expression of STAT-3, which induces upregulation of TGF $\alpha$  and ICAM-1
- Secrete IL-1, TNF $\alpha$ , IL-6, IL-8 (chemoattractant)

- **Genetics (polygenic and multifactorial)**

- HLA associations:
  - Cw6 (strongest) associated with early onset
  - B13, DR7, B17, B57 associated with earlier onset
  - B27 associated with psoriatic arthritis
  - A2 and Cw2 (weaker association)

B13, B17, Cw6: guttate psoriasis

- In moderate to severe psoriasis, ↑ risk of cardiovascular disease; other comorbidities may include hypertension, obesity, dyslipidemia, diabetes mellitus; common genetic factors (B27) may also cause ↑ incidence of inflammatory bowel disease
- Triggering factors
  - Physical trauma (Köebner phenomenon)
  - Infection (especially streptococcal pharyngitis)
  - Stress
  - Medications (most commonly associated listed below)
    - Lithium
    - $\beta$ -blocker
    - Antimalarial
    - ACEI
    - NSAID
    - Withdrawal of systemic corticosteroid
    - G-CSF
    - Interferon
- **Chronic plaque psoriasis** presents with erythematous, scaly sharply-bordered macules, papules and plaques covered with silvery scale over extensor surfaces (knees, elbows), scalp, gluteal cleft,  $\pm$  genitalia,  $\pm$  intertriginous areas; chronic course with flares



**Figure 3.6**

**A: Plaque psoriasis**

**B: Plaque psoriasis**

(Courtesy of Dr. Paul Getz)

**C: Guttate psoriasis**

- **Guttate psoriasis** (Figure 3.7A) presents with acute-onset rain drop-like scaly papules on the trunk and extremities often in young patients; frequently preceded by streptococcal infection and eruption usually resolves completely within few months (may turn into chronic plaque psoriasis in adults)
- Special locations:
  - Palms and soles (**palmoplantar psoriasis**)
  - Intertriginous areas (**inverse psoriasis**)
- **Psoriatic nails** (Figure 3.7B): may affect nail matrix, bed or plate; may be sole involvement or part of extensive disease
  - Pitting (nail matrix → focal parakeratosis in nail plate)
  - Leukonychia (nail matrix)
  - Onychodystrophy (nail matrix ± bed → subungual hyperkeratosis)
  - Oil spots (nail bed → yellow brown spots)
  - Onycholysis (nail bed → separation of plate from bed)
  - Splinter hemorrhages (↑ capillary fragility in nail bed)
- **Erythroderma** (Figure 3.7C)
  - Generalized erythema and scaling (>90% skin surface affected), ± leukocytosis, ↑ ESR, lymphadenopathy; may develop suddenly from guttate or stable psoriasis but typically due to inappropriate treatment of disease
- Histology: confluent parakeratosis (focal parakeratosis in guttate), hyperkeratosis, collection of neutrophils in stratum corneum (Munro microabscesses) and spinous layer (spongiform pustules of Kogoj), hypogranulosis, acanthosis with clubbed rete ridges, suprapapillary thinning, dilated blood vessels in papillary dermis, perivascular lymphocytes
- Treatment:
  - Topicals
    - Vitamin D3 analogues (i.e. calcipotriol, calcipotriene)
    - Corticosteroids
    - Calcineurin inhibitors (pimecrolimus/tacrolimus for intertriginous areas)
    - Tazarotene
    - Coal tar
    - Anthralin
    - Fixed combination betamethasone dipropionate/calcipotriol
  - Oral
    - Acitretin
    - Methotrexate
    - Cyclosporine
  - Other
    - Biologic agents
    - Phototherapy (PUVA, NBUVB)
    - Excimer laser

Topical calcipotriene may be inactivated in acidic environment (i.e. salicylic acid)



**Figure 3.7**  
**A: Guttate psoriasis**  
**B: Psoriasis involving nail**  
**C: Erythrodermic psoriasis**  
 (Courtesy of Dr. Paul Getz)



**Pustular Psoriasis (Figure 3.8A–C)**

- Distinct from psoriasis vulgaris in both features and clinical course
- ↑ HLA-B27 incidence
- Two types: generalized and localized (palmoplantar pustulosis, acrodermatitis continua suppurativa)
- **Generalized (von Zumbusch)**
  - Presents initially with malaise and fever, subsequent onset of erythematous macules studded with sterile pustules; initially in intertriginous areas but quickly spreads to trunk, extremities and nails (skin feels painful), ↑ risk for infection
  - Risk factors: tapering oral corticosteroid, infection, hypocalcemia, pregnancy (impetigo herpetiformis)
  - Labs: leukocytosis, hypoalbuminaemia
  - Treatment: correct electrolyte and protein imbalance, methotrexate or cyclosporine (avoid systemic corticosteroid), later treatment can include phototherapy or biologic treatment
- **Palmoplantar pustulosis**
  - Tense, sterile pustules over palmoplantar surface with yellow-brown macules; may be associated with SAPHO syndrome (so prudent to inquire about any sternoclavicular tenderness and/or back pain)
  - Treatment: acitretin, topical corticosteroid
- **Acrodermatitis continua of Hallopeau**
  - Variant of pustular psoriasis limited to finger tip or digit; HLA-B27 association
  - Presents with sterile pustules on erythematous base at tip of finger (less likely on toe) forming lakes of pus, associated pain and impaired use of digit; if pustules within nail bed, nail will typically be shed; may have loss of bony structures
  - Treatment: topical calcipotriene, topical corticosteroid, acitretin

**Psoriatic Arthritis (Table 3-3)**

- Up to 30% of patients with psoriasis have arthritis; associated with moderate to severe psoriasis and typically occurs several years after appearance of skin lesions
- Rheumatoid factor negative (seronegative) arthritis; HLA-B27 association
- Tendons and ligaments often involved (enthesopathy or enthesitis) in addition to bone and cartilage
- ↑ TNF $\alpha$  level in synovium and serum in patients with psoriasis and psoriatic arthritis
- Almost all patients with psoriatic arthritis have nail changes (up to 20% may have no skin findings)
- Common features include pain at tendon insertion sites, digital involvement and sacroiliac disease, asymmetric joint involvement, negative rheumatoid factor, morning stiffness lasting more than 1 hour
- Treatment: TNF $\alpha$  antagonists, methotrexate, NSAID, cyclosporine, sulfasalazine

**Figure 3.8****A: Pustular psoriasis****B: Palmoplantar psoriasis\*****C: Palmoplantar psoriasis\***

\*Courtesy of Dr. Paul Getz

**Table 3-3 Forms of Psoriatic Arthritis**

Type of Arthritis	%	Salient Features
Asymmetric oligoarthritis	70%	Single or multiple <u>distal joints in hands or feet</u> involved; synovitis and joint swelling, $\pm$ swelling of digit (dactylitis or 'sausage finger'); knees, ankles and sometimes axial involvement (if HLA-B27 positive) may also occur
Asymmetrical DIP arthritis	5–10%	Single or multiple DIP joint involvement; periarticular swelling with concomitant nail involvement
Symmetrical polyarthritis (RA-like)	15%	Involvement of small and medium-sized joints (PIP, MCP, wrists, elbows); difficult to distinguish from rheumatoid arthritis (RA); usually seronegative
Spondylitis and sacroiliitis	5%	Typically in men and resembles ankylosing spondylitis, with addition of knee and sacroiliac involvement, $\pm$ peripheral joint involvement, $\pm$ inflammatory bowel disease or uveitis, often positive for HLA-B27
Arthritis mutilans	5%	Digits become shorter, wider, softer due to osteolysis of phalanges and metacarpals; results in telescoping motion of digits

X-ray findings: 'pencil in cup' deformity (distal head of bone appearing sharpened like a point), **fusiform tissue swelling** ('sausage digit'), **tuft resorption**, **eccentric erosions**

### Reiter's Disease (Reactive Arthritis) (Figure 3.9)

- Seronegative arthropathy with constellation of symptoms
- Linked to two factors
  - Genetic factor: HLA-B27
  - Exposure to pathogen
    - May follow urethritis after exposure to GU pathogens (likely *Chlamydia trachomatis*)
    - May follow GI infection after exposure to enteric pathogens such as *Campylobacter* spp., *Shigella flexneri*, *Ureaplasma urealyticum*, *Salmonella* spp., or *Yersinia* spp.
- Bacterial antigen mimics portion of HLA molecule with subsequent dysregulation of immune control mechanism
- More common and severe in HIV patients; may be presenting sign of HIV
- Presentation
  - Peripheral arthritis  $\geq 1$  month duration, with
  - Associated urethritis or cervicitis
  - Other findings: urethritis, conjunctivitis, fever weakness, weight loss, erythema nodosum



**Figure 3.9**

**A: Circinate balanitis**

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009)



- Skin findings in 5% patients: psoriasiform lesions similar to psoriasis
  - Keratoderma blenorrhagicum: thick plaques with pustules and erythema on plantar surfaces
  - Circinate balanitis: circinate erythematous lesions on glans penis (almost pathognomonic)
- Classic triad: urethritis, arthritis, conjunctivitis
- Treatment: treatment of any triggering infection (doxycycline 100 mg bid × 14 days); arthritic symptoms may treat with biologic agent, methotrexate, cyclosporine, acitretin or NSAID; cutaneous lesions with high-potency topical corticosteroid

### Pityriasis Rubra Pilaris (PRP)

- Disorder of keratinization with bimodal distribution involving children and adults, nearly always acquired (occasional familial cases described)
- Presents with
  - Hyperkeratotic follicular papules on erythematous base, which coalesce into large orange-red to red patches with characteristic 'islands of sparing'
  - Palms and soles with waxy orange-red keratoderma
  - May rapidly evolve into erythroderma
  - Nail changes include subungual hyperkeratosis and nail plate thickening
- 5 types:
  - Type I and II in adults, Type III–V in children (see Chap. 2 for pediatric types)
    - Type I (classic): over half of all cases; sudden onset of symptoms with duration of 2–5 years
    - Type II (atypical): about 5% cases, slow onset with alopecia, localized lesions and chronic course
- Histology: acanthosis, thickened granular layer, 'checkerboard parakeratosis' (orthokeratosis alternating with parakeratosis both vertically and horizontally), 'shoulder parakeratosis' adjacent to follicular plugs, perivascular lymphocytic infiltrate
- Treatment: high potency topical corticosteroid, systemic retinoid, methotrexate, ± phototherapy, azathioprine, infliximab

## B. LICHENOID DERMATOSES

### Lichen Planus (Figures 3.10A–C, 3.11A–C, Table 3-4)

- Pruritic papular disease of skin and mucous membranes
- Due to cell-mediated autoimmune reaction toward basal layer keratinocytes; may be idiopathic, drug-related or infection-related (HCV)
- 4P's: papular, pruritic, polygonal, purple
- Often lasts 1–2 years (except oral and hypertrophic forms, which typically have protracted courses)



**Figure 3.10**

**A: Annular lichen planus**

(Courtesy of Dr. Paul Getz)

**B: Blaschkoid lichen planus**

(Courtesy of Dr. Iris K. Aronson)

**C: Oral lichen planus** (Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases*. London: Springer; 2008)

**Table 3-4 Types of Lichen Planus**

Type	Description
<b>Acute LP</b>	Eruptive lichenoid papules with wide distribution, heals with hyperpigmentation; self-limited (typically resolves within 9 months)
<b>Actinic LP</b>	Photosensitive variant of LP with melasma-like appearance or lichenoid papules over face, neck and dorsal hands; typically in children and young adults with spring or summer onset (some consider entity as lichenoid form of polymorphous light eruption {PMLE})
<b>Annular LP</b>	Annular papules and plaques with central clearing (commonly over penis)
<b>Atrophic LP</b>	Lichenoid papules replaced with depressed atrophic areas typically over lower legs, ± residual hyperpigmentation; resembles lichen sclerosus clinically
<b>Bullous LP</b>	Vesicles and bullae arising within existing LP lesions (intense inflammatory reaction at dermoepidermal junction causes subepidermal bullae)
<b>Drug-induced LP</b>	Distribution typically generalized or sun-exposed sites; Wickham's striae uncommon; ± eosinophils and parakeratosis on histology; medication typically taken for several months before eruption appears  Common meds: <b>β-blockers, captopril, penicillamine, HCTZ, antimalarials, furosemide, quinidine, NSAID, tetracycline, quinacrine, gold, sulfonyleureas, hydroxyurea, methyldopa</b>
<b>Erosive or ulcerative LP</b>	Painful, chronic, recalcitrant erosive lesions especially on oral mucosa and palmoplantar surface; small ↑ risk of SCC within longstanding lesions; erosive oral LP associated with <b>liver disease (HCV)</b>
<b>Genital LP</b>	Seen in up to 20% of LP patients; glans penis common site for men (annular lesions, small grouped papules, or larger plaques); vulvar LP commonly erosive and may coexist with gingival involvement ('vulvovaginal gingival syndrome')
<b>Hypertrophic LP</b>	Thick, hyperkeratotic intensely pruritic plaques commonly found over shins or dorsal feet; also known as LP verrucosus
<b>Inverse LP</b>	LP lesions in groin, axillae and inframammary regions
<b>Linear LP</b>	Linear groups of lichenoid papules following lines of Blaschko
<b>Mucosal LP</b>	Up to 50% patients with skin disease may have oral mucosal changes; ranges from reticular, atrophic, erosive, bullous, papular to pigmented; reticular type most common with lacy white hyperkeratosis on buccal mucosa, lips, tongue and gingiva; typically asymptomatic unless erosive; rarely may see esophageal, laryngeal or conjunctival involvement
<b>Nail LP</b>	10% of LP patients; may be isolated finding; typically lateral nail thinning, longitudinal ridging, <b>dorsal pterygium</b> , splitting, ± 20 nail dystrophy
<b>LP/LE overlap</b>	Clinical and histologic features of both lupus erythematosus (LE) and LP
<b>Palmoplantar LP</b>	Painful hyperkeratotic yellow to erythematous plaques on palms and soles (lateral borders and pressure points), ± ulceration, erosions; recalcitrant to therapy
<b>LP Pemphigoides</b>	Tense vesicles and bullae arise in normal, uninvolved skin; typically blisters occur weeks to months after appearance of typical LP lesions; overlap between bullous pemphigoid and LP; + IgG antibody to <b>BP180 (NC16A)</b>  <b>DIF: linear IgG/C3 at BMZ IIF: IgG at roof of blister (salt-split skin)</b>
<b>LP Pigmentosus</b>	Gray-brown macules in sun-exposed areas ± flexural folds in darker-skinned patients; similar to erythema dyschromicum perstans
<b>Lichen planopilaris</b>	Keratotic follicular papules with violaceous rim leading to cicatricial alopecia  <b>Graham-Little-Piccardi-Lasseur syndrome: typical skin/mucous membrane LP, scarring alopecia of scalp, nonscarring loss of pubic/axillary hairs</b>

- Presents with intense pruritus and violaceous, smooth flat-topped papules and plaques with fine scale (Wickham's striae) over flexor wrists, forearms, legs, presacrum and other areas, + Koebner phenomenon
- No conclusive evidence to support association with autoimmune disease (per Bologna); difficult to determine if true HLA association
- Histology
  - Hyperkeratosis (without parakeratosis)
  - ↑ Granular layer
  - Partially effaced rete ridges with widened papillae ('sawtooth' appearance)
  - Vacuolar change of basal layer with colloid bodies
  - Band-like lymphocytic infiltrate at dermoepidermal junction
  - Dermal melanophages
- Treatment: superpotent topical corticosteroids, topical calcineurin inhibitors, intralesional or systemic corticosteroid, phototherapy, methotrexate, acitretin, oral metronidazole (latter for erosive oral form)

### Lichenoid Keratosis

- Likely due to inflammation of lentigo, actinic keratosis or seborrheic keratosis
- Brown to red scaly papule on sun-exposed extremity
- Solitary lesion mimicking lichen planus histologically

### Graft-Versus-Host Disease (GVHD) (Figure 3.12A–C)

- Clinical syndrome resulting from the transfer of immunologically competent cells to an immunosuppressed host
- Donor lymphocytes recognize the recipient as 'foreign' and mount an immunological attack primarily against the skin, mucosa, gastrointestinal tract and liver
- Histocompatibility (both major and minor complexes) between the donor and host is the most important factor in the development of GVHD



**Figure 3.11**

**A: Lichen planus, lips\***

**B: Lichen planus, palmoplantar\***

**C: Lichen planus, genital\***

*\*Courtesy of Dr. Paul Getz*



- One of the major complications of allogeneic hematopoietic stem cell transplantation (can also occur after transfusion of unirradiated blood products or donor lymphocytes in setting of solid organ transplantation)
- Two forms (acute and chronic GVHD) based on time of presentation since transplant date (part of same spectrum)
- **Acute GVHD**
  - Occurs within first 100 days following transplantation (typically within 1–3 weeks after transplantation)
  - Presents with a maculopapular eruption which may coalesce into confluent erythema ( $\pm$  evolve into erythroderma or bullae resembling toxic epidermal necrolysis); acral erythema with violaceous discoloration of pinna of ear suggestive
  - Triad of dermatitis, enteritis with diarrhea, and hepatitis with abnormal LFTs,  $\pm$  high fever, conjunctival erythema
  - Histology: vacuolization of basal layer, necrotic keratinocytes, sparse perivascular or interface dermatitis,  $\pm$  complete epidermal necrosis (severe cases)
  - Course: 30–50% of patients with moderate to severe acute GVHD die
  - Treatment: systemic corticosteroid
- **Chronic GVHD**
  - Occurs after mean of 4 months (as early as 40 days)
  - Evolves from acute GVHD in approximately 50% surviving patients, otherwise *de novo*
  - Divided into early lichenoid and late sclerodermoid
    - **Lichenoid GVHD:** violaceous to erythematous lichenoid papules over dorsal hands, forearms, trunk and may become widespread,  $\pm$  mucous membrane involvement (lacy white plaques or erosions in mouth, salivary gland involvement with Sjögren-like syndrome)
    - **Sclerodermoid GVHD:** sclerotic plaques similar to morphea,  $\pm$  hyperpigmentation,  $\pm$  sicca symptoms, may also involve the gastrointestinal tract, lungs, liver and musculoskeletal system
  - Main cause of death of chronic GVHD: infection due to immunosuppression
  - Histology: chronic lichenoid GVHD similar to lichen planus; sclerodermoid GVHD with epidermal atrophy and dermal fibrosis
  - Treatment: topical calcineurin inhibitor, PUVA, UVB, prednisone, hydroxychloroquine, cyclosporine, mycophenolate mofetil, azathioprine, photopheresis



**Figure 3.12**

**A: GVHD, acute\***

**B: GVHD, acute\***

\* Reprint from Morgan MB, Smoller BR, Somach SC, *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007

**C: GVHD, chronic**

(Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)



## C. ECZEMATOUS DERMATOSES

**Atopic Dermatitis:** see Chap. 2

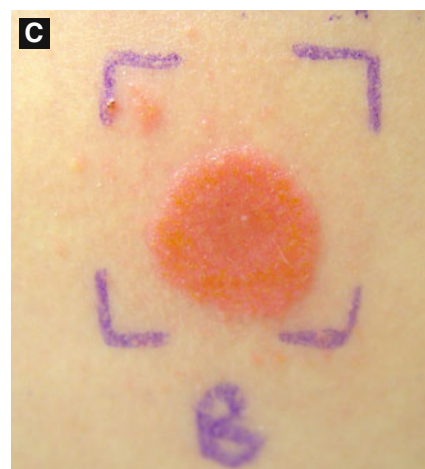
**Contact Dermatitis (CD)** (Figure 3.13A-B, Tables 3-5 to 3-8)

- Acute or chronic inflammatory reaction to a substance in contact with the skin; divided into irritant and allergic CD
- **Irritant contact dermatitis (ICD)**
  - Accounts for 80% of CD
  - Due to direct local cytotoxic effect of irritant on skin
  - **Acute ICD:** acute exposure to toxic agent; presents with pruritus and sharply localized erythema with vesicles, edematous papules or hemorrhagic blisters,  $\pm$  scaling or crusting; no distant spread
  - **Chronic ICD:** repeated exposure to mild irritants (low-grade irritation); presents with diffuse or localized but ill-defined scaly patches and plaques
- **Allergic contact dermatitis (ACD)**
  - Accounts for 20% of all CD
  - Type IV delayed hypersensitivity to contactant (to which already sensitized), onset may be delayed as long as 24–96 h after allergen exposure
  - Nickel and poison ivy (urushiol) most common causes of ACD
  - Patch testing (Figure 3.13C) is the gold standard for diagnosing ACD; grading system:

Reaction	Description
+	Weak reaction with erythema, infiltration, $\pm$ papules
++	Strong reaction: <b>vesicles</b> , erythema, infiltration, papules
+++	Spreading bullous reaction

- **Poral reaction:** non-allergic reaction due to cobalt residing in acrosyringium
- **Acute ACD:** typically presents 24–48 h after exposure and presents with pruritus, vesicles, weeping and erythema,  $\pm$  dissemination of lesions
- **Subacute ACD:** presents with eczematous scaly plaques or lichenification correlating to areas of contact with allergen
- Histology: spongiosis, intraepidermal vesicles and superficial perivascular infiltrate in acute setting; acanthosis, hyperkeratosis and mild superficial infiltrate in chronic setting
- Treatment: avoid exposure irritants/allergens; topical corticosteroid, patch testing (for ACD), if severe may use short-term systemic corticosteroid

Factors	ACD	ICD
Previous exposure required	Yes	No
Immunologic reaction	Yes	No
Distant spread	Yes	No
Dose-related response	No	Yes
Similar reaction in others w/ exposure	No	Yes



**Figure 3.13**

**A:** Allergic contact dermatitis  
(Courtesy of Dr. Paul Getz)

**B:** Subacute contact dermatitis

**C:** Patch testing, 2+ reaction

(Courtesy of Dr. Sophie M. Worobec)

**Table 3-5 Contact Allergens**

Formaldehyde-Releasing Preservatives		
Quaternium-15	Most common cosmetic preservative to cause ACD; personal care products	
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	Formaldehyde-releasing preservative in personal care products and variety of industrial applications	
Diazolidinyl urea (Germall II)	Formaldehyde-releasing preservative; personal care products (especially bubble baths, baby wipes and household detergents)	
Imidazolidinyl urea (Germall 115)	Formaldehyde-releasing antimicrobial preservative used in cosmetics	
DMDM hydantoin	Formaldehyde-releasing antimicrobial preservative used in cosmetics like shampoo, hair conditioners and skin care products	
Rubber accelerators		
Thiuram	Rubber in shoes, rubber gloves, elastic, fungicides, paints, barrier contraceptives	Thiuram cross reacts w/ <b>disulfiram</b>
Mercaptobenzothiazole (MBT)	Most common cause of <b>allergic shoe dermatitis</b>	
	Rubber products, tires, antifreeze, anticorrosive agents, cutting oils, electrical cords, fungicides, rubber shoes (sneakers, tennis shoes, etc.)	
Carba mix	Leather shoes, tires, fungicides, cosmetic applicators, gloves, adhesives, elastic, barrier contraceptives; may cross react with thiuram derivatives	
	Repeated washing of elastic (ie. undergarments) with hypochlorite (bleach) causes elastic to become more allergenic (due to ↑ availability of carbamates), which may result in ‘elastic dermatitis’ or ‘bleached rubber syndrome’ (but patch test negative for rubber accelerators)	
Mercapto mix	Tires, elastic, rubber gloves, electrical cords, rubber soles of shoes, etc.	
Black rubber mix	Heavy-use rubber products such as tires, hoses, cables and belts	
Mixed dialkyl thioureas	Neoprene rubber (wetsuit), goggles, elastic, paint remover, shoe insoles	
Textiles		
Disperse blue 106	Clothing dye (bed linens, blue dye, clothing, tights, garment lining)	
Ethylene urea melamine formaldehyde mix	Permanent press clothing (wrinkle-resistant)	Textile dermatitis typically occurs where clothing fits tightly (posterior neck, upper back, lateral thorax, axillae, waistband, flexor surfaces); ± <b>purpuric contact dermatitis</b>
Adhesives		
Epoxy resin (bisphenol A)	Glues, plastics, electrical insulation, paint and primer	
Colophony (rosin, abietic acid)	Paper, cosmetics, paint, adhesives, waxes, chewing gum, used in baseball/ ballet/musical instruments to ↑ friction	
Cyanoacrylate (methyl or ethyl)	Fast-acting adhesive ( <b>Super</b> or <b>Krazy Glue</b> ), liquid bandages, <b>Dermabond</b>	
Ethyl acrylate	Artificial nail (adhesive)	
Methacrylate (methyl or ethyl)	Adhesive, <b>artificial nails</b> , <b>dental fillings/sealants</b> , hearing aids, hard contact lenses, glue (bone cement) for <b>artificial joints</b> , acrylic denture material	
	May <b>diffuse through intact surgical glove</b> and cause <b>paresthesias</b> (i.e. most commonly seen in either dentist or orthopedic surgeon)	
p-tert-butylphenol formaldehyde resin	Leather/rubber adhesive	
Sunscreen components		
Benzophenone-3	Sunscreens, rubber products, cosmetics	
PABA (Padimate O)	Sunscreen (UVB)	PABA ± cross react w/ <b>sulfonamides</b> , <b>azo dyes</b> , <b>benzocaine</b> , <b>PPD</b>
Oxybenzone	Sunscreen (UVA)	<b>Oxybenzone</b> : most common sunscreen agent to cause <u>photoallergic contact dermatitis</u>
Continued on the next page		

*Continued on the next page*

**Table 3-5 Contact Allergens (cont'd)**

Corticosteroids	
Tixocortol-21-pivalate	Group A (hydrocortisone acetate, prednisone, methylprednisolone)
Budesonide	Group B (triamcinolone acetonide, desonide, fluocinolone acetonide, fluocinonide, halcinonide) Budesonide also marker for some Gr. D steroids
Hydrocortisone-17-butyrate	Group D (hydrocortisone-17-valerate/butyrate, clobetasone-17-butyrate, clobetasol propionate, betamethasone valerate/dipropionate)
Hair preparations	
Paraphenylenediamine (PPD)	Permanent hair dye, 'black henna' (not natural henna from plant), photographic developer, printing inks, black rubber, temporary tattoos ACD typically on eyelids/ear helices/hairline or hands May cross react with: <b>PABA</b> , <b>sulfonamides</b> (including thiazide and furosemide), para-aminosalicylic acid, <b>benzocaine</b> and <b>procaine</b> (ester anesthetics), azo dyes (temporary/semi-permanent hair dye, pen ink, coloring agent)
Monothioglycolate	Permanent wave preparations; typically in glycerol monothioglycolate
Ammonium persulfate	Hair bleach, bleaching agent in flour
Others	
Bacitracin	Topical antibiotic ointment, otic and ophthalmic preparations
Balsam of Peru	Naturally occurring fragrance material, found in topical medications
Benzalkonium chloride	Skin disinfectant (ophthalmic solutions), cosmetics
Benzocaine, tetracaine	Local anesthetic (ester) May cross-react with <b>PABA</b> , <b>PPD</b> , and <b>sulfonamides</b>
Cobalt	Added to other metals to ↑ hardness; found in jewelry, buttons, cosmetics, hair dye, joint replacements, ceramics, enamel, cement, paint, and pottery
Cocamidopropyl betaine	Hair and bath products like shampoo (surfactant)
Ethylenediamine	Medical creams, antifreeze, paint Cross-reacts with <b>hydroxyzine</b> and <b>aminophylline</b>
Euxyl K400	Cosmetic and household products (preservative)
Fragrance mix	Several components ( <i>cinnamic aldehyde</i> ), detects 70% fragrance allergies
Formaldehyde	Textile resins ( <b>wrinkle-free clothing</b> ), cosmetics, tissue fixative, embalming solution, paints, disinfectants, and medications
Gold	Jewelry, dentistry, electronics, treatment of certain diseases (RA, SLE, etc.)
Glutaraldehyde	Cold sterilization (medical/dental equipment), disinfectant, tan shoe leather
Lanolin (wool alcohol)	Cosmetics and some topical creams
Methylchloroisothiazolinone (Kathon CG)	Preservative in cosmetics and shampoos (antibacterial properties)
Neomycin sulfate	Antibiotic ointment, hemorrhoidal cream, otic and ophthalmic preparations Co-sensitivity often between neomycin and bacitracin
Nickel sulfate	Costume jewelry, buckles, and snaps; <b>dimethylglyoxime</b> test detects nickel (positive if turns pink); ± co-sensitivity seen with nickel and <i>cobalt</i>
Paraben mix	Cosmetics, topical medications, food, textiles, antiperspirants
Potassium dichromate	Cement, leather (footwear), plaster, wood finishes, green felt of card tables
Propylene glycol	Cosmetics, topical medications (vehicle), antifreeze
Thimerosal	Preservative in contact lens solution, vaccines, otic/ophthalmic solution, antiseptic ↑ photosensitivity with piroxicam if patient with positive reaction to thimerosal
Tocopherol acetate	Vitamin E
Toluene sulfonamide	Nail polish (typically appears as eyelid dermatitis or periungual dermatitis)

Also known as  
tosylamide  
sulfonamide  
formaldehyde resin

**Table 3-6 Plant Allergens**

Allergen	Plant (Common Name)	Scientific Name
<b>Urushiol</b> (includes pentadecacatechol in oleoresin)	Poison ivy, poison sumac, poison oak	Family: Anacardiaceae
		Genus: Toxicodendron; Species: Rhus
	May cross react with <b>Japanese lacquer tree</b> (sap), <b>cashew tree, mango tree, Indian marking nut</b> (black juice), <b>Brazilian Pepper tree</b> (sap), <b>gingko</b> (seed pulp)	
<b>Sesquiterpene lactone</b>	Chrysanthemum, ragweed, sunflower, artichoke, arnica, daisy, marigold, arnica	Family: Asteraceae or Compositae
		May cross react with <b>permethrin</b>
	Dermatitis may be <b>airborne</b> (face, neck) or direct contact (hands)	
<b>Primin</b>	Primrose	Family: Primulaceae
		Species: Primula obconica
<b>Diallyl disulfide, allylpropyl disulfide</b>	Garlic, onion, chives	Family: Alliaceae
		Genus: Allium
<b>Allicin</b>	Garlic, onion, chives	Family: Alliaceae
		Genus: Allium
<b>Tuliposide A</b>	Peruvian lily	Family: Alstroemeriaceae
	Tulip, hyacinth	Family: Liliaceae
<b>d-Usnic acid</b>	Lichens	Several genera including Parmelia
<b>Colophony</b> (Abietic acid, rosin)	Pine tree (resin)	Family: Pinaceae
		Species: Pinus species
<b>Tea tree oil</b> (Limonene)	Ti or tea tree	Family: Myrtaceae
		Species: Melaleuca alternifolia
<b>3-carene</b>	Turpentine	Family: Pinaceae

**Table 3-7 Plant Irritants (ICD)**

Irritant	Plant
<b>Bromelin</b>	Pineapple (Ananas comosus)
<b>Calcium oxalate</b>	Dumb cane (Araceae), daffodils (Narcissus spp.), hyacinth (Liliaceae), pineapple
<b>Phorbol esters</b> (in milky latex)	Poinsettias, spurges, crotons (Euphorbiaceae)
	May cause temporary blindness if latex contacts eye
<b>Capsaicin</b>	Chili peppers (Solanaceae)
<b>Thiocyanates</b> (Allyl isothiocyanate)	Garlic (Alliaceae)
	Black mustard and radish (Brassicaceae)
<b>Protoanemonin</b> (Ranunculin)	Buttercups (Ranunculaceae)
	Causes intense linear vesiculation      Ranunculin converts to protoanemonin after plant injury



**Table 3-8 Pigment Reactions from Tattoos**

Tattoo Color	Chemical
Black	Carbon, iron oxide
Blue	Cobalt
Brown	Ferric oxide
Green	Chromic oxide
Purple	Manganese
Red	<b>Cinnabar</b> (mercury sulfide), cadmium red
White	Titanium dioxide
Yellow	<b>Cadmium sulfide</b>

Most common allergic reaction seen from **red tattoo pigment**

### 3.3 GRANULOMATOUS, METABOLIC AND DEPOSITIONAL DISEASES

#### A. GRANULOMATOUS DISEASES

##### Granuloma Annulare (GA) (Figure 3.14A–C)

- Asymptomatic, benign and self-limited granulomatous disease of the dermis seen in both adults and children
- Unknown etiology; may include trauma and sun exposure
- Presents as skin-colored to pink non-scaly papules coalescing into annular or arciform plaques, typically over dorsal hand or foot; variants listed below:

GA Variant	Description
<b>Patch GA</b> (Macular)	Patches of erythema typically over extremities ± trunk
<b>Generalized GA</b> (Disseminated)	Flesh-colored pink papules over trunk/extremities; poor response to treatment; association with <b>diabetes</b>
<b>Perforating GA</b>	Small papules with central umbilication and crusting (discharging necrotic collagen) typically over dorsal hands
<b>Subcutaneous GA</b>	Deep dermal nodules similar to rheumatoid nodules; typically asymptomatic

- Histology: necrobiotic foci in dermis surrounded by histiocytes (palisading granulomas) or histiocytes splayed between collagen bundles (interstitial type), mucin accumulation, ± perivascular lymphocytes/eosinophils
- Treatment: clinical observation as typically self-limited (50–75% of cases with resolution in 2 years) in localized GA, potent topical corticosteroid or intralesional corticosteroid

##### Necrobiosis Lipoidica ± Diabeticorum (NLD) (Figure 3.15A, B)

- Uncommon necrobiotic disease associated with diabetes mellitus (DM): 30–40% patients with NLD have DM, but only 0.03–3% of patients with DM manifest with NLD
- Presents with yellow to red-brown atrophic to indurated plaques typically over pretibial areas; prominent telangiectasias, ± ulceration
- Histology: normal to atrophic epidermis, histiocytes often encircling necrobiotic collagen in dermis in layered fashion (tier-like, parallel to epidermis), ± sclerosis, interstitial lymphocytes, plasma cells, histiocytes, and multinucleated giant cells (granulomatous inflammation)

**Horizontal palisading sandwiches** and plasma cells on histology (unlike GA)



**Figure 3.14**

**A: Granuloma annulare**  
**B: Granuloma annulare**  
 (Courtesy of Dr. Paul Getz)  
**C: Subcutaneous GA**  
 (Courtesy of Dr. Paul Getz)

- Treatment: high potency topical corticosteroid (1st line) or IL injection into active border; aspirin + dipyridamole (to ↓ plt aggregation), niacinamide, and if severe refractory ulcerations consider excision with graft

### Annular Elastolytic Giant Cell Granuloma (Actinic Granuloma)

- Unclear if distinct disease or variant of GA
- ± Related to inflammation triggered by actinic damage
- Presents as annular erythematous plaque with slightly atrophic center in sun-exposed areas of older adults; tendency for slow spread
- Histology: solar elastosis, absence of elastic fibers in center of lesion, elastic fibers adjacent to or within giant cells (elastophagocytosis), granulomatous inflammation
- Treatment: topical corticosteroids (inconsistent response)

### Necrobiotic Xanthogranuloma (NXG) (Figure 3.15C)

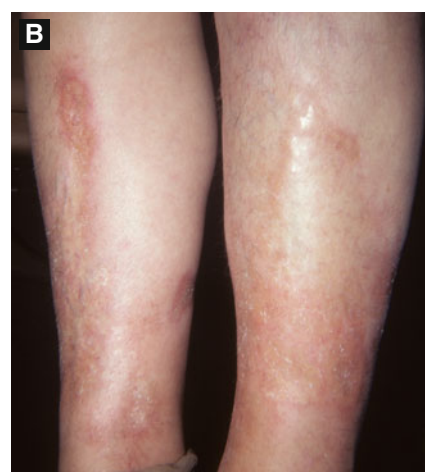
- Rare, multisystem histiocytic disease
- Presents as red-orange to yellow papules, nodules or plaques on face (periorbital), tendency toward ulceration
- 80% with IgG monoclonal gammopathy (↑ risk of plasma cell dyscrasias and lymphoproliferative disorders)
- Histology: mid-dermal palisading xanthogranuloma with areas of necrobiotic, degenerated collagen that infiltrates the mid-dermis with extension into the subcutaneous fat; foamy histiocytes, plasma cells, giant cells (Touton and bizarre foreign body), and cholesterol clefts within granulomas

### Cutaneous Crohn's Disease

- Skin changes related to Crohn's disease
- **Genital:** labial or scrotal erythema with swelling
- **Nongenital:** erythematous indurated plaque or ulcerations with drainage (typically perianal)
- **Oral:** cobblestoning (buccal mucosa), small aphthae-like ulcers or linear ulcers, pyostomatitis vegetans, cheilitis glandularis, indurated fissuring of lower lip
- Histology: non-caseating granulomas (sarcoidal or diffuse)
- Treatment: topical or IL corticosteroid

### Foreign Body Granuloma (Tables 3-9, 3-10)

- Immune response to exogenous or endogenous material that has wounded skin
- Histology: ranges from sarcoid-like granulomatous reaction, necrobiotic reaction, suppurative reaction to reaction consisting of mild fibrosis



**Figure 3.15**

**A: Necrobiosis lipoidica**

(Courtesy of Dr. Sophie M. Worobec)

**B: Necrobiosis lipoidica**

(Courtesy of Dr. Paul Getz)

**C: Necrobiotic xanthogranuloma**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**Table 3-9 Properties of Foreign Bodies**

Doubly Refractile with Polarized Light (Birefringent)		PAS Positive
Silica (dirt or glass)	Talc (deodorant/powdered gloves)	Starch
Wood splinter	Sutures (nylon)	Plant material
Starch	Keratin (hair shafts)	
Spines of sea urchins		

**Table 3-10 Common Foreign Body Reactions**

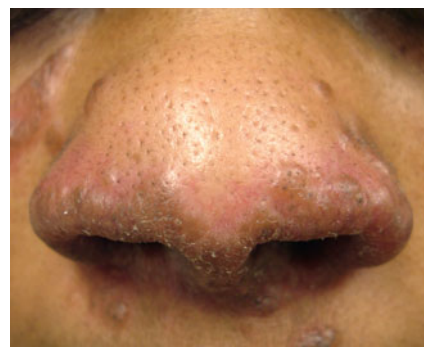
Foreign Body	Clinical Findings	Histological Reaction
<b>Intralesional corticosteroid</b>	Yellowish to skin-colored nodule at site of injection	Foreign body granuloma with pale blue (mucin-like) acellular material in center
<b>Keratin</b>	Erythematous follicular papules (i.e. acne keloidalis nuchae)	Foreign body granuloma, $\pm$ fragments of keratin (section of hair shafts, birefringent)
<b>Suture material</b>	Erythematous papule or papules	Birefringent basophilic suture fibers in dermis with surrounding foreign body granuloma
<b>Tattoo pigment</b>	Lichenoid papules, eczematous dermatitis, erythema or induration	Extracellular pigment (typically black) with foreign body reaction (only if allergic reaction)
<b>Wood splinter</b>	Erythema, induration or papule	Brownish color with prominent cell walls (honeycomb appearance) surrounded by granulomatous inflammation; birefringent
<b>Silica, zirconium, beryllium</b>	Erythema, induration or papule	Foreign body granuloma, sarcoidal granuloma or caseating granuloma; doubly refractile spicules
<b>Silicone</b>	Nodule, indurated plaque, or ulceration	'Swiss cheese' appearance due to presence of silicone-filled cavities surrounded by histiocytes (may be multinucleated or foamy)
<b>Hyaluronic acid</b>	Erythema, induration, papule or nodule	Basophilic amorphous material, stains with Alcian blue
<b>Paraffin</b>	Firm indurated nodule or plaque, $\pm$ ulceration	'Swiss cheese' appearance (stains with oil red O)
<b>Starch</b>	Indurated nodule typically	Maltese cross configuration with polarized light
<b>Monsel's solution</b>	Clinically consistent with nevus or tattoo	Brown black deposits (containing iron) in dermis due to ferrous subsulfate



**Sarcoidosis** (Figures 3.16 and 3.17A, B)

- Chronic multisystem inflammatory disease characterized by non-caseating granulomas of unknown etiology
- Related to ↑ activity of cell mediated immune system
- ↑ Frequency and severity in African American patients
- Presents with cutaneous findings in approximately 30–40% patients, may be sole or initial manifestation
- Presents typically with non-scaly, skin-colored to red-brown circinate or annular infiltrated papules/plaques on face, lips, neck, trunk, extremities; cutaneous sarcoidosis may develop within pre-existing scars
  - Hypopigmented lesions not uncommon in African-American patients
  - Sarcoidal plaques may appear psoriasiform
  - Less common presentations include ichthyosis over lower legs, hypopigmentation, scarring alopecia, and ulcerations
  - Variants (listed below)
- Histology: superficial and deep sharply-defined naked epithelioid granulomas, giant cells, minimal lymphocytes near granulomas, eosinophilic stellate inclusion bodies (**asteroid bodies**) or round basophilic laminated inclusions (**Schaumann bodies**) seen in giant cells
- Diagnosis (of exclusion): supported by ↑ ACE, ↑ calcium, ↑ ESR
- Treatment: topical, IL or systemic corticosteroid, hydroxychloroquine, methotrexate or other immunosuppressant

Sarcoidosis Variant	Clinical Findings
<b>Lupus pernio</b>	Violaceous doughy infiltration on nose, cheeks or earlobes; often associated with chronic sarcoidosis of lungs, chronic uveitis and bone cysts; chronic course
<b>Darier-Roussy disease</b>	Also known as sarcoidal panniculitis; painless subcutaneous mobile nodules without epidermal change
<b>Löfgren's syndrome</b>	Acute sarcoidosis; erythema nodosum, hilar adenopathy, acute iritis, migrating polyarthritis, and fever
<b>Mikulicz syndrome</b>	Complex of symptoms caused by a variety of systemic disorders (i.e. Sjögren syndrome, lymphoma and sometimes sarcoidosis) Parotid and lacrimal enlargement with swelling, ± sicca symptoms
<b>Parinaud oculoglandular syndrome</b>	Conjunctivitis with ipsilateral lymphadenopathy Also caused by infection (cat-scratch fever or tularemia)
<b>Heerfordt's syndrome</b>	'Uveoparotid fever'; fever, parotid gland enlargement, anterior uveitis, facial nerve palsy
<b>Erythema nodosum</b>	Seen in acute or subacute sarcoidosis; <b>good prognostic sign</b> , associated with transient sarcoidosis that resolves spontaneously
<b>Oral sarcoidosis</b>	May involve mucosa, tongue, major salivary glands, hard palate and gingival tissue
<b>Ocular sarcoidosis</b>	Seen in 15–25%: anterior uveitis (common), <b>lacrimal gland involvement</b> , chronic uveitis leading to adhesions, glaucoma, and blindness
<b>Non-mucocutaneous findings</b>	Lung disease (alveolitis, fibrosis, hilar adenopathy), liver, spleen, bone, kidney, heart, GI involvement; hypercalcemia



**Figure 3.16**  
**Sarcoidosis**  
(Courtesy of Dr. Iris K. Aronson)



**Figure 3.17**  
**A: Sarcoidosis**  
(Courtesy of Dr. Paul Getz)  
**B: Sarcoidosis, hypopigmented**



## B. METABOLIC AND DEPOSITIONAL DISEASES

### Amyloidosis (Figure 3.18)

- Refers to several diseases sharing common feature of abnormal deposition of eosinophilic amyloid protein in various tissues
- Amyloid properties: insoluble fibril protein aggregates with  $\beta$ -pleated sheet configuration
- Classified into systemic and organ-limited amyloidosis, with the former being associated with  $\uparrow$  morbidity and mortality (unlike the cutaneous counterpart)
- Histology: deposits of eosinophilic, homogenous and amorphous material limited to papillary dermis with melanin incontinence in lichen/macular amyloidosis; waxy eosinophilic fissured nodules involving dermis in nodular amyloidosis; characteristic staining pattern showing green birefringence under polarized light with Congo red stain; other stains include methyl violet, crystal violet, PAS + (diastase resistant), Sirius red, pagoda red 9, scarlet red (RIT), and thioflavin T



**Figure 3.18**  
**Lichen amyloidosis**  
(Courtesy of Dr. Paul Getz)

**Table 3-11 Types of Cutaneous Amyloidosis**

Type	Description	Protein
<b>Macular amyloidosis</b>	Presents with hyperpigmented small firm papules in rippled appearance coalescing into thin plaques, typically over interscapular region; asymptomatic or moderately pruritic; $\pm$ associated notalgia paresthetica <u>Treatment</u> : potent topical corticosteroid, topical capsaicin	<b>Keratinocyte-derived</b>  Seen in MEN type 2A
<b>Lichen amyloidosis</b>	Presents with small, flat-topped shiny papules typically over shins, highly pruritic <u>Treatment</u> : reduce friction, potent topical corticosteroid $\pm$ occlusion or IL corticosteroid, phototherapy	<b>Keratinocyte-derived</b>  Seen in MEN type 2A
<b>Nodular amyloidosis</b>	Presents with single or multiple waxy nodules $\pm$ purpura on limbs or trunk Can progress to <b>systemic involvement</b> in about <b>7%</b> cases $\rightarrow$ long term follow up needed <u>Treatment</u> : excision or laser ablation if few lesions	<b>AL</b> (immunoglobulin light chains, typically $\lambda$ )
<b>Secondary amyloidosis</b>	Amyloid deposits seen both in benign and malignant cutaneous tumors	<b>Keratinocyte-derived</b>

**Multiple endocrine neoplasia (MEN) type 2A** (Sipple syndrome): RET gene, AD  
Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism,  $\pm$  **lichen or macular amyloidosis**

Of note, MEN type 1 (Wermer syndrome) associated with **facial angiofibromas**, **collagenomas** and **lipomas**  
Type 2B (aka type 3) associated with **mucosal neuromas**

Table 3-12 Types of Systemic Amyloidosis

Type	Description/Treatment	Protein
<b>Primary systemic amyloidosis</b>	Usually associated with <b>underlying plasma cell dyscrasia</b> ; up to 50% may have mucocutaneous lesions including macroglossia ( $\pm$ indentation of teeth), difficulty swallowing, <b>ecchymosis</b> and <b>'pinch' purpura</b> due to vessel fragility from perivascular amyloid deposition ('raccoon eyes'), waxy nodules and plaques, <b>bullous lesions</b> (especially hemorrhagic); hoarseness; other non-cutaneous involvement include carpal tunnel syndrome, RA-like arthropathy, <b>shoulder pad sign</b> (amyloid infiltration around periarticular soft tissue), cardiac arrhythmias, heart failure, restrictive cardiomyopathy; may be associated with multiple myeloma; confirmation of diagnosis in absence of cutaneous findings with aspiration of abdominal fat to detect amyloid deposits (fat pad aspiration)	<b>AL</b> (light chain)
<b>Secondary systemic amyloidosis</b>	Amyloid deposition in organs due to underlying <b>chronic inflammatory or infectious process</b> (i.e. rheumatoid arthritis, tuberculosis, chronic abscess, periodic fever syndromes such as <b>familial Mediterranean fever</b> , <b>TRAPS</b> and <b>Muckle-Wells syndrome</b> – see below); skin typically not involved	<b>AA</b> (non-immunoglobulin protein: amyloid-associated)
<b>Hemodialysis-associated amyloidosis</b>	Due to $\uparrow$ secretion of <b><math>\beta</math>2-microglobulin</b> in patients with <b>long-term hemodialysis</b> ; deposition in synovial membranes resulting in <b>carpal tunnel syndrome</b> and spondyloarthropathy	<b>A<math>\beta</math>2M</b> ( <b><math>\beta</math>2-microglobulin</b> )
<b>Familial amyloidosis</b>	Includes familial amyloidotic polyneuropathy, AD inheritance; findings include peripheral and autonomic neuropathy; treatment: orthotopic liver transplantation (remove major source of TTR)  TTR transports thyroxine and retinol	<b>ATTR</b> (TTR or <b>transthyretin</b> )
<b>Senile systemic amyloidosis</b>	Late-onset disease seen in elderly patients due to deposition of TTR-derived amyloid fibrils in heart causing CHF, cardiomyopathy	<b>ATTR</b> ( <b>transthyretin</b> or TTR)

**Muckle-Wells syndrome** (MWS): CIAS1 mutation (encodes cryopyrin), AD  $\rightarrow$  urticaria, deafness, renal amyloidosis, acute attacks of fever, abdominal pain, myalgias, arthralgias, and conjunctivitis; treat w/ glucocorticoids or anakinra (recombinant human IL-1 receptor antagonist)

**Familial Mediterranean fever** (FMF): MEFV mutation (encodes pyrin, also known as marenostrin), AR  $\rightarrow$  recurrent episodes of polyserositis, fever, erysipelas-like erythema (legs); treat w/ colchicine (prophylaxis)

**TNF receptor associated periodic syndrome** (TRAPS): TNFR1 mutation, AD  $\rightarrow$  high fever, erythematous annular or serpiginous patches/plaques on extremities, abdominal pain, arthralgias/myalgias; treat w/ TNF inhibitors or glucocorticoids

## Mucinoses

- Heterogenous group of skin disorders involving abnormal accumulation of mucin
- Mucin
  - Mixture of acid glycosaminoglycans normally produced in small amounts by fibroblasts
  - Routine H&E shows blue-staining material between collagen bundles or empty space

Special stains for mucin: Alcian blue, colloidal iron or toluidine blue

**Table 3-13 Forms of Mucinoses**

Type	Description/Treatment
<b>Scleromyxedema</b>	<p>Presents with generalized symmetric eruption of several waxy firm papules accompanied by induration and thickening of the skin (sclerodermoid) with ↓ mobility; typically involves hands, forearms, face ('leonine facies'), neck, thighs and upper trunk; associated with <b>monoclonal gammopathy</b> (paraproteinemia) <b>IgG λ</b> (lambda light chain); due to fibroblast proliferation and mucin deposition in dermis; non-cutaneous manifestations include myopathy, arthropathy, neuropathy, dysphagia, lung and renal disease; poor prognosis</p> <p><u>Treatment</u>: disappointing; stem cell transplant, oral immunosuppressants (including thalidomide), electron beam therapy; of note, monthly melphalan used in past but associated with ↑ mortality</p>
<b>Lichen myxedematosus</b> (Papular mucinosis)	<p>Localized form of scleromyxedema (spectrum) with small, flat-topped shiny papules mainly over extensor extremities; does not progress to scleromyxedema but shows little tendency for spontaneous resolution</p> <p><u>Treatment</u>: observation or topical corticosteroid</p>
<b>Scleredema</b> (Scleredema of Buschke) (Scleredema diabeticorum)	<p>Three forms:</p> <ul style="list-style-type: none"> <li>– <u>Infection-related</u>: preceding fever, malaise and infection (typically <b>streptococcal</b>) in children and women; presents with induration of cervicofacial area with extension to proximal extremities and trunk; typically self-limited</li> <li>– <u>Gammopathy-related</u>: similar to above but with insidious onset and without preceding infection; typically associated with <b>monoclonal gammopathy</b></li> <li>– <u>Diabetes-related</u>: subtle onset erythema and induration of neck and back (± <i>peau d'orange</i> appearance) in obese men with <b>IDDM</b>; persistent involvement</li> </ul> <p>All three may have some form of systemic involvement: dysphagia, cardiac abnormalities, serositis</p> <p><u>Treatment</u> (for latter two types): phototherapy, cyclophosphamide, oral glucocorticoid, cyclosporine</p>
<b>Reticular erythematous mucinosis</b> (REM)	<p>Erythematous macules and papules in reticulated pattern over midline chest and back; may be induced by UV light</p> <p><u>Treatment</u>: antimalarials, sun protection</p>

## Porphyria

- Inherited or acquired disorders due to enzyme deficiency causing ↑ production of porphyrins (photosensitizing) or their precursors during heme synthesis

Porphyrins (uroporphyrin, coproporphyrin, protoporphyrin) absorb light intensely in the **Soret band (400–410 nm)** → reactive oxygen species with subsequent damage to skin, liver, and/or rbc's

**Table 3-14 Types of Porphyria**

Inheritance/Defect	Labs	Description	Treatment
Congenital Erythropoietic Porphyria (CEP) (Gunther’s disease)			
AR <u>Uroporphyrinogen III cosynthase</u>	Urine: ++ uro/copro Stool: ++ copro RBC: + uro Plasma: + fluoresce	Extreme photosensitivity (bullae with subsequent mutilated scarring), hypertrichosis, <b>erythrodontia</b> (red fluorescent teeth), hemolysis, red urine (stains diapers), ↑ risk skin CA	Light avoidance, transfusions for anemia, ± bone marrow transplantation (BMT), ± splenectomy
CEP: Colorless (anemia), Erythrodontia, Photosensitivity UTC (uro three cosynthase): Ur Teeth r Colored			
Erythropoietic Protoporphyrria (EPP)			
AD <u>Ferrochelatase</u>	Urine: normal levels Stool: ++ proto RBC: ++ proto Plasma: ± fluoresce	Photosensitivity with burning, heals with waxy scars, porphyrin <b>gallstones, hepatic damage</b>	Light avoidance, oral β-carotene, monitor liver
EPP: enzyme starts with F			
Porphyria Cutanea Tarda (PCT)			
AD (familial form) or acquired <u>Uroporphyrinogen decarboxylase</u> (UD)	Urine: ++ uro > copro Stool: + isocopro RBC: normal levels	Tense bullae, erosions, milia and scarring on sun-exposed skin, hypertrichosis (temples), iron overload, scleroderma-like changes, facial hyperpigmentation	Phlebotomy every 2 weeks, oral antimalarial agent
PCT – UD: Urine Dazzles pink (fluoresce with Wood’s light)		Triggers: alcohol, HCV, estrogen, polychlorinated hydrocarbons, iron overload (hemochromatosis, C282Y gene), HIV	
Acute Intermittent Porphyria (AIP)			
AD <u>Porphobilinogen deaminase</u> (PBD)	Urine: + ALA, PBG, Stool/RBC/plasma: all normal levels	NO skin findings; neurologic and psychiatric findings w/ ↑ abdominal pain	Remove trigger, glucose loading, hematin infusion
AIP-PBD: Abdomen Is Painful, Please Barbiturates D/C		Triggers: drugs (barbiturates), stress, fasting, alcohol, hormonal changes, infections	
Variegate Porphyria (VP)			
AD <u>Protoporphyrinogen oxidase</u> (PPO)	Urine: + ALA/PBG Stool: + proto, copro Plasma: + fluoresce	Overlap between AIP and PCT VP-PPO: ViPs have Pink Plasma Optimized at 626 nm (fluoresces)	Same treatment for AIP during acute attacks
Hereditary Coproporphyria			
AD <u>Coproporphyrinogen oxidase</u> (CPO)	Urine: ALA, PBG, Stool: + copro, proto RBC: normal level	Acute attacks similar to mild version of AIP; may have skin findings (mimics PCT)	Same as variegate prophyria
Hepatoerythropoietic Porphyria			
AR <u>Uroporphyrinogen decarboxylase</u>	Urine: + uro Stool: + uro, copro RBC: + proto	Overlap between PCT and CEP	Photoprotection (phlebotomy NOT effective)

Uro: uroporphyrinogen Copro: coproporphyrinogen Isocopro: isocoproporphyrinogen  
Proto: protoporphyrinogen ALA: aminolevulinic acid PBG: porphobilinogen



**Calciophylaxis (Calcific Uremic Arteriopathy)** (Figure 3.19)

- Rare condition of systemic calcification involving small and medium-sized vessels with ischemic necrosis of the skin and soft tissue; high mortality
- Presents initially as painful violaceous mottling (reticulated) typically on lower extremities → stellate purpura with central necrosis, ± central bulla, followed by necrosis and ulceration; death due to gangrene and sepsis
- Most commonly in patients with end-stage renal disease on hemodialysis or after renal transplant with elevated calcium-phosphate product
- Treatment
  - Normalization of calcium-phosphate product (by low calcium dialysis)
  - Sodium thiosulfate (↑ solubility of calcium deposits)
  - Bisphosphonates (pamidronate, etridonate)
  - Calcimimetics (cinacalcet)
  - Parathyroidectomy
  - Wound therapy

**Figure 3.19****A: Calciophylaxis**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**Familial Hyperlipidemias**

- See Table 3-15

**Table 3-15 Types of Familial Hyperlipidemia**

Type	Defect	↑ CAD Risk	Serum	Lipid Levels	Clinical Findings
<b>Type I</b> Familial LPL deficiency Familial hyperchylomicronemia	↓ Lipoprotein lipase (LPL) or apoprotein CII defect	No	<b>Creamy top layer</b>	↑↑ TG (chylomicrons)	<b>Eruptive xanthomas, acute pancreatitis</b> abdominal pain, lipemia retinalis
<b>Type IIa</b> Familial hypercholesterolemia Familial defective apo B100	LDL receptor defect (mutation of LDLR or apo B)	Yes	Clear	↑↑ Cholesterol (LDL)	<b>Tendinous and tuberous xanthomas, xanthelasma</b>
<b>Type IIb</b> Familial combined hypercholesterolemia	LDL receptor defect	Yes	Clear or cloudy	↑ Cholesterol ↑ TG (LDL, VLDL)	<b>Tendinous and tuberous xanthomas, xanthelasma</b>
<b>Type III</b> Familial dysbetalipoproteinemia	Apoprotein E defect	Yes	Turbid	↑ Cholesterol ↑ TG (IDL, VLDL)	<b>Xanthoma striatum palmare, tuberous xanthomas</b> pathognomonic
<b>Type IV</b> Familial hypertriglyceridemia	↑ Production of VLDL	±	Turbid	↑ TG (VLDL, IDL)	<b>Eruptive xanthomas;</b> associated with DM, obesity, alcoholism
<b>Type V</b>	Apolipoprotein C-II defect	±	Creamy top layer	↑↑ TG ↑ Cholesterol (VLDL, chylo)	<b>Eruptive xanthomas, acute pancreatitis</b> abdominal pain

**Table 3-16 Types of Xanthomas (Figure 3.20A–C)**

Type of Xanthoma	Description
Tuberous xanthomas (seen in type II, III)	Pink-yellow papulonodules on extensor pressure surfaces, especially knees/elbows; slow to regress after initiation of treatment; seen in <b>hypercholesterolemic</b> states
Tendinous xanthomas (II, III)	Smooth nodular lipid deposits of the <b>Achilles tendon</b> > extensor tendons of hands, knees or elbows; may also see in hepatic cholestasis secondary to <b>primary biliary cirrhosis</b>
Plane xanthomas (II, III)	Yellow slightly elevated plaques typically involving eyelids, <b>trunk, neck, shoulder or axillae</b> ; may also be from <b>biliary cirrhosis</b> ; if normolipemic, may be associated with <b>monoclonal gammopathy (IgG)</b>  Intertriginous almost pathognomonic for homozygous familial hypercholesterolemia
Xanthoma striatum palmare (III)	Type of plane xanthoma over palm with yellow-orange infiltration of volar creases (palms and fingers), characteristic for <b>type III</b>
Xanthelasma (II, III)	Plane xanthoma of eyelid; yellow flat-topped papules or plaques around medial eyelids; only half of patients with hyperlipidemia
Eruptive xanthomas (I, IV, V)	Eruption of small yellow papules with erythematous base on back, <b>buttocks</b> , chest, and proximal extremities; seen in <b>hypertriglyceridemic</b> state (often >3,000 mg/dl); associated with diabetes, pancreatitis, chronic renal failure  Do not confuse with xanthoma disseminatum

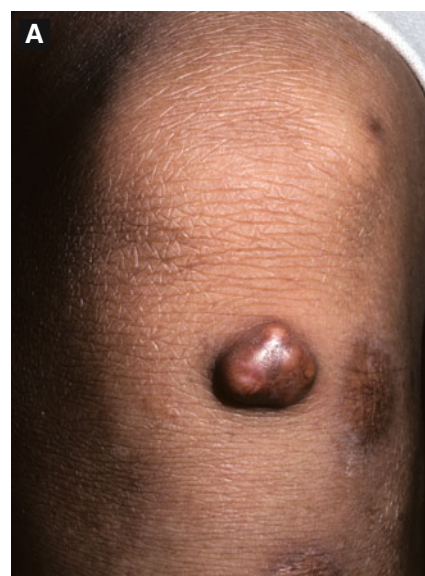
Xanthoma disseminatum: occurs in **normolipemic** patients; red-yellow papules with flexural predilection

### Gout

- Recurrent attacks of acute inflammatory arthritis
- Due to hyperuricemia → deposition of needle-like crystals of monosodium urate in skin and joints
- Presents with firm, skin-colored to white-yellow dermal or subcutaneous papules or nodules (tophi), ± ulcerated surface with drainage of chalky material or white flecks
- Negative birefringence under polarized light

### Pseudogout

- Deposits of calcium pyrophosphate dihydrate (CPPD) crystals within joints
- Weakly positive birefringence under polarized light

**Figure 3.20****A: Tuberous xanthoma\*****B: Tendinous xanthoma\*****C: Eruptive xanthoma\***

\*Courtesy of Dr. Paul Getz

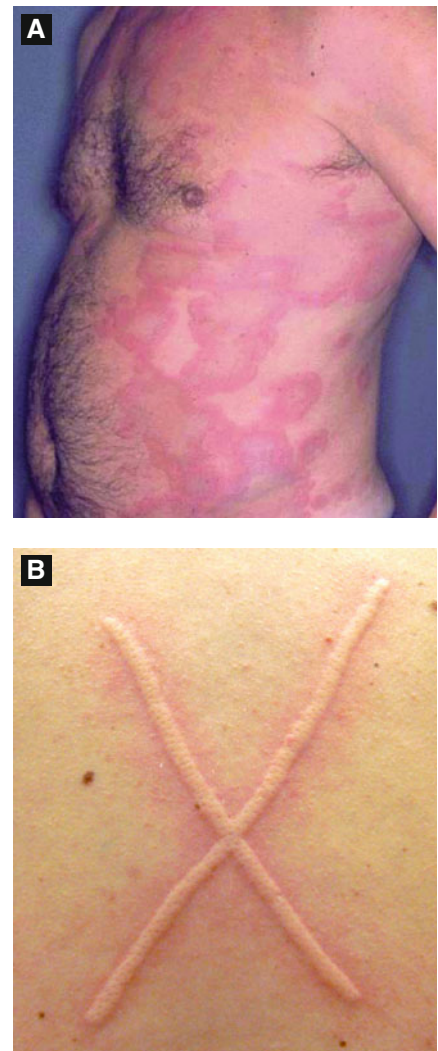
### 3.4 ERYTHEMAS AND PURPURAS

#### A. ERYTHEMAS

##### Urticaria (Figure 3.21A, B)

- Discrete pink areas of swelling involving either superficial skin or mucosa with associated pruritus; lesions last < 24 h, ± associated angioedema
- Acute urticaria < 6 weeks, chronic > 6 weeks
- Urticaria due to cross-linking of two or more high affinity IgE receptors (FcεRI) with subsequent release of mast cell storage granules:
  - Newly formed mediators: prostaglandin D2, leukotriene C4/D4/E4, platelet-activating factor (PAF)
  - Preformed: histamine, heparin, tryptase, chymase
- Causes: idiopathic, immunologic, non-immunologic
  - Immunologic
    - IgE-mediated type I hypersensitivity (allergic)
    - Immune complex deposition (serum sickness)
    - Complement-dependent
    - Autoantibodies: anti-IgE or anti-FcεRI antibodies (most often seen in chronic urticaria)
  - Non-immunologic (direct/indirect degranulation)
    - Drugs (opiates, radiocontrast dye, polymyxin B, aspirin, NSAID), contact-induced (i.e. nettle stings), certain foods
- Histology: perivascular infiltrate of scant eosinophils and lymphocytes (sometimes neutrophils), ± eosinophils splayed between collagen bundles, ± dermal edema
- Treatment: remove trigger; antihistamine (H1), ± short course of oral corticosteroid; if chronic urticaria consider lab work (CBC, ESR, ANA, anti-IgE/FcεRI antibodies, anti-thyroid antibodies, stool ova/parasite)

Type of Urticaria	Description
Dermographism	Urticarial lesions resulting from light scratching
Delayed pressure urticaria	Deep swelling with overlying erythema at sites of sustained pressure occurring with a delay of up to 12 h
Cholinergic urticaria	Small erythematous papules appearing within 15 min of sweat-inducing stimulus (i.e. physical exercise)
Solar urticaria	Occurs typically <b>within minutes</b> of exposure to sun (UV or visible light), lasts for <1 h, may have accompanying <b>headache</b> and <b>syncope</b>
Aquagenic urticaria	Eruption after contact with water, typically lasts for <1 h
Cold urticaria	Urticaria in cold-exposed areas (often seen when skin rewarmed)
Contact urticaria	Urticaria at site of contact (i.e., nettle stings, latex)



**Figure 3.21**

**A: Urticaria**

(Reprint from Misery L, Stander S, eds. *Pruritus*. London: Springer; 2010)

**B: Dermographism**



**Angioedema (Without Urticaria)** (Figure 3.22A, B)

- Deep form of urticaria with localized non-pitting edema
- Presents with episodes of painful deep swelling of subcutaneous tissue (especially periorbital/lips), GI tract (abdominal pain) and upper respiratory tract (laryngeal edema), lasts > 24 h (usually few days)
- Etiology: idiopathic, drug-related (NSAID, ACEI) or abnormality of C1 inhibitor (C1-INH)

ACEI: results in unregulated generation of bradykinin

- C1-INH: serine protease inhibitor, prevents spontaneous activation of complement system
- **Hereditary angioedema (HAE)**
  - Autosomal dominant
  - C1-INH deficiency
    - Type 1: ↓ C1-INH level
    - Type 2: normal/↑ C1-INH level, but dysfunctional
  - Presents in 1st or 2nd decade
  - Labs: ↓ C4, ↓ C1-INH (level and/or function); C1q normal
  - Histology: perivascular lymphocytic infiltrate and dermal edema
  - Treatment: C1-INH concentrate during acute attack (of note, antihistamine, epinephrine, corticosteroid → not typically effective); fresh frozen plasma (FFP) before surgery; prophylactic treatment with attenuated androgens like danazol and stanazolol
- **Acquired C1 inhibitor deficiency (AAE)**
  - Usually seen after fourth decade, no family history; due to destruction of C1-INH function through either immune complexes or autoantibodies
  - Presentation similar to HAE
    - Type 1: associated with lymphoproliferative disorders (i.e. B cell lymphoma, multiple myeloma, non-Hodgkin's lymphoma) with significant amounts of immune complexes consuming C1q
    - Type II: associated with autoimmune phenomenon with autoantibodies to C1-INH molecule
  - Both AAE types with ↓ C1q (unlike HAE), ↓ C4/C2
  - Treatment: requires much higher amounts of C1-INH concentrate than in HAE during acute attack

Type	C1-INH Level	C1-INH Function	C4	C1q
<b>HAE, type 1</b>	↓	↓	↓	Normal
<b>HAE, type 2</b>	Normal to ↑	↓	↓	Normal
<b>AAE, type 1</b>	↓	↓	↓	↓
<b>AAE, type 2</b>	↓	↓	↓	↓

**Figure 3.22****A: Angioedema**

(Courtesy of Dr. Paul Getz)

**B: Hereditary angioedema**

(Reprint from Bork K, Barnstedt S.

Laryngeal edema and death from

asphyxiation after tooth extraction in four patients with hereditary angioedema.

JADA 2003;1088–94. Copyright ©2003

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**Erythema Annulare Centrifugum (EAC)** (Figure 3.23A)

- Figurate erythema due to infection (especially dermatophyte), medication, neoplasm or idiopathic
- Presents with annular or polycyclic erythematous plaques with ‘trailing’ scale at inner border, infiltrated peripheral border; expands centrifugally with central clearing
- Histology: focal parakeratosis, superficial and deep perivascular mononuclear infiltrate with characteristic ‘cuffing’ or ‘coat sleeving’ fashion
- Treatment: treat any underlying disorder, topical corticosteroid

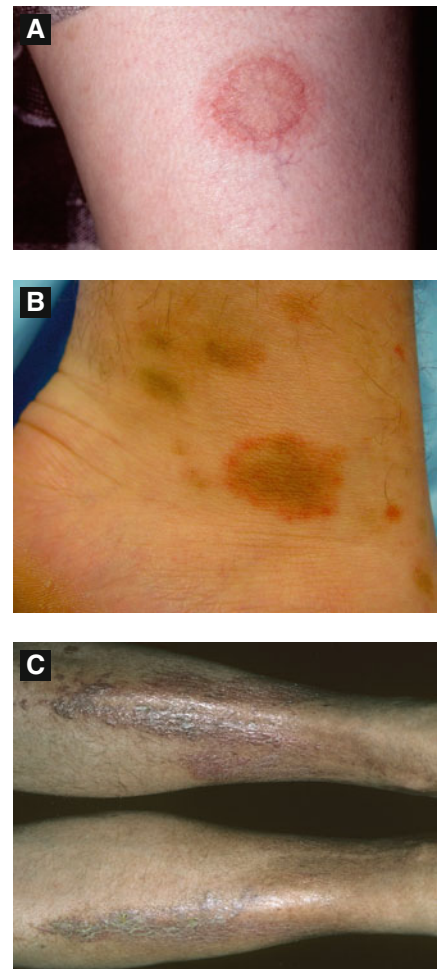
**Erythroderma**

- Generalized erythema with scaling, ± systemic manifestations (tachycardia, loss of fluid/protein, etc.)
- Several etiologies including atopic dermatitis, psoriasis, cutaneous T cell lymphoma (CTCL) or drug reaction
- Histology/treatment: dependent on underlying cause

**B. PURPURAS****Pigmented Purpuric Dermatoses** (Figure 3.23B, C)

- Group of dermatoses with capillaritis and petechial hemorrhages often in background of yellow discoloration due to hemosiderin deposition
- Distribution/pattern varies according to specific variant
- Histology: red cell extravasation, hemosiderin, perivascular lymphocytic infiltrate, ± lichenoid infiltrate in both lichen aureus and lichenoid dermatitis of Gougerot-Blum
- Treatment: ascorbic acid + rutoside, ± phototherapy, compression stockings if accompanying venous stasis, topical corticosteroid if pruritus

Variants	Description
<b>Schamberg’s disease</b> (Progressive pigmentary dermatosis of Schamberg)	Discrete clusters of pinpoint erythematous nonblanching macules typically on lower legs → coalesce into patches with overall appearance of ‘cayenne pepper’; older lesions appear tan to brown
<b>Majocchi’s disease</b> (Purpura annularis telangiectodes)	Annular erythematous plaques with punctate telangiectasias typically in young adults (more common in women)
<b>Pigmented purpuric lichenoid dermatitis of Gougerot and Blum</b>	Lesions similar to Schamberg’s disease plus red-brown lichenoid papules and plaques
<b>Lichen aureus</b>	Typically solitary rust to purple-colored patch or plaque on lower extremity with golden hue
<b>Eczematid-like purpura of Doucas and Kapetanakis</b>	Scaly purpuric or petechial macules, patches and papules

**Figure 3.23****A: EAC***(Courtesy of Dr. Paul Getz)***B: Majocchi’s disease***(Courtesy of Dr. Sophie M. Worobec)***C: Pigmented purpuric lichenoid dermatitis***(Courtesy of Dr. Paul Getz)*

### 3.5 VESICULOBULLOUS DISEASES (Figures 3.29, 3.30, Table 3-17)

#### Immunofluorescence (IF) techniques:

<b>Direct IF (DIF)</b>	Detects <i>in vivo</i> antibodies bound to tissue antigens in <b>perilesional skin</b>
<b>Indirect IF (IIF)</b>	Detects circulating <b>serum antibodies</b> (substrate sections react with serially diluted serum from patient → incubated with anti-IgG or other specific fluorescent dye-tagged antibody)  <b>Best substrate: monkey esophagus (PV), guinea pig esophagus (PF), transitional rat bladder epithelium (PNP)</b>
<b>Salt-split-skin (SSS) technique</b>	Variant of IIF allowing <b>distinction</b> between <b>different subepidermal</b> blistering conditions with <b>similar DIF findings</b> ; normal human skin incubated in 1 M NaCl for 48–72 h resulting in split at <b>lamina lucida</b> level; location of antibody binding to split ( <b>epidermal or dermal side</b> ) distinguishes different diseases

#### **Pemphigus Vulgaris (PV)** (Figures 3.24A–C and 3.25A)

- Potentially fatal autoimmune bullous disease of the skin and mucous membranes
- **Autoantigen:** cadherin family, desmosomal protein
  - Desmoglein 3 (mucosal)
  - Desmoglein 1 (mucocutaneous)
- **Clinical:** flaccid vesicles/bullae which rupture leaving large, painful erosions with bleeding and crusting; erosions may also be in nose, mouth, larynx, pharynx, vagina; + Nikolsky sign, + Asboe-Hansen sign (pressure to surface of blister causes lateral spread)
  - **Pemphigus vegetans** (variant of PV): vegetating plaques in scalp and intertriginous areas; histology similar to PV + pseudoepitheliomatous hyperplasia, ↑↑ inflammatory cell infiltrate, intraepidermal microabscesses with eosinophils and neutrophils
- **Drug-induced:** thiol drugs (penicillamine, captopril, enalapril, lisinopril, piroxicam), pyrazolone derivatives (phenylbutazone, oxyphenylbutazone), antibiotics (penicillin derivatives, cephalosporin, rifampicin)
- **Histology:** suprabasal cleavage with acantholytic keratinocytes, ‘tombstone row’ of basal cells attached to basement membrane, perivascular lymphocytes and eosinophils, acantholysis may involve hair follicles
- **DIF:** intercellular IgG4 ≥ C3 (net-like pattern in epidermis, more pronounced in lower epidermis)
- **IIF:** monkey esophagus, + in 80–90% cases, titer correlates with disease activity
- **Treatment:** oral corticosteroid, methotrexate, azathioprine, mycophenolate mofetil, plasmapheresis, IVIG, rituximab

Associations: **HLA-DR4, HLA-DRw6, HLA-DR14**



**Figure 3.24**

**A: Pemphigus vulgaris**  
(Courtesy of Dr. Iris K. Aronson)  
**B: Pemphigus vulgaris**  
(Courtesy of Dr. Iris K. Aronson)  
**C: Pemphigus vulgaris**  
(Courtesy of Dr. Paul Getz)

**Pemphigus Foliaceus (PF)** (Figure 3.25B)

- Less severe and more superficial than PV
- **Autoantigen:** desmoglein 1 Dsg 1 also in striate PPK
- **Clinical:** flaccid bullae which rupture easily; often only erythematous patches, erosions, and crusting remain
  - **Fogo selvagem** (endemic form of PF): seen in rural Brazil and clinically identical to PF, related to the black fly (*Simulium spp.*)
  - **Pemphigus erythematosus** (Senear-Usher syndrome): localized PF variant with lupus erythematosus overlap; involves seborrheic areas with erythema, erosions and crusting; ANA positive in 30%; DIF: intercellular and linear IgG at BMZ; treat with sun protection, oral/topical corticosteroid
- **Drug-induced:** penicillamine, nifedipine, ACEI
- **Histology:** subcorneal acantholysis with acantholytic cells seen on blister roof ('clinging ons'), neutrophils can be seen in blister cavity (resembling impetigo)
- **DIF:** same as PV (more pronounced in upper layers)
- **IIF:** + in 80% cases, best substrate is guinea pig esophagus
- **Treatment:** similar to PV

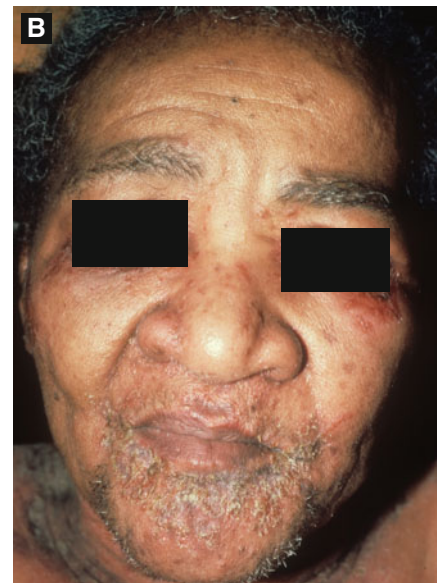
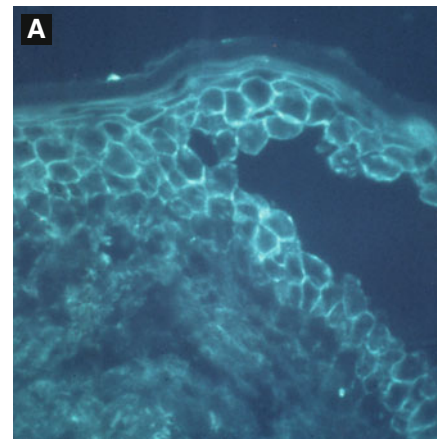
**Paraneoplastic Pemphigus (PNP)** (Figure 3.25C)

- Associated with underlying benign or malignant neoplasm: non-Hodgkin's lymphoma (most common), chronic lymphocytic leukemia, Castleman's disease, thymoma, Waldenström macroglobulinemia, sarcoma

Two benign diseases: Castleman's disease and benign thymoma

- **Autoantigen:** various desmosomal proteins including desmoglein 3, periplakin, envoplakin, desmoplakin 1/2, BPAG1, plectin, 170 kDa Ag, rarely desmoglein 1
- **Clinical:** severe stomatitis that extends onto vermillion lip; intraorally can involve entire oropharynx; cutaneous presentation varies considerably from lichenoid papules, flaccid or tense bullae, erythematous macules to erythema-multiforme-like lesions on hands/ft; conjunctivae, perianal and genital region may develop painful erosions
- **Histology:** suprabasilar acantholysis, ± vacuolar basal layer damage associated with lichenoid dermal lymphocytic infiltrate, and necrotic keratinocytes
- **DIF:** intercellular + linear IgG/C3 along BMZ
- **IIF:** intercellular IgG, best substrate is rat bladder epithelium (most sensitive)
- **Treatment:** stomatitis refractory to treatment and immunosuppressive agents less effective than for PV; prognosis associated with underlying neoplasm

Binds **rat bladder transitional epithelium** unlike PV



**Figure 3.25**

**A:** DIF, pemphigus vulgaris

(Courtesy of Dr. Paul Getz)

**B:** Pemphigus foliaceus

(Courtesy of Dr. Paul Getz)

**C:** Paraneoplastic pemphigus



### IgA Pemphigus

- Blistering disease with intraepidermal IgA deposits
- **Autoantigen:** desmocollin 1 (SPD),  $\pm$  desmoglein 1/3 (IEN)
- **Clinical:** two types
  - **Subcorneal pustular dermatosis (SPD):** seriginous vesicles or pustules; may be associated with underlying IgA gammopathy
  - **Intraepidermal neutrophilic type (IEN):** flaccid pustules and bullae involving intertriginous locations which enlarge forming annular or polycyclic (sunflower-like) arrangement
- **Histology:** intraepidermal pustule or vesicles containing neutrophils, no acantholysis
- **DIF:** intercellular IgA deposition (unlike SCDP of Sneddon-Wilkinson)
- **IIF:** + in 50%, intercellular IgA
- **Treatment:** dapsone, oral corticosteroid

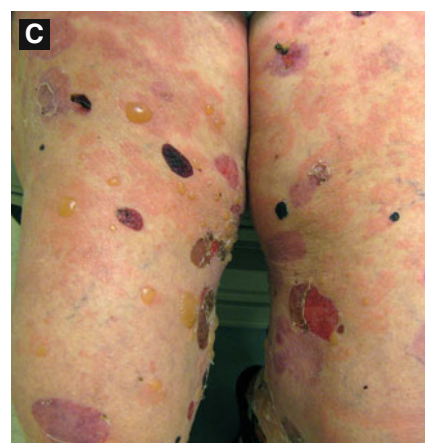
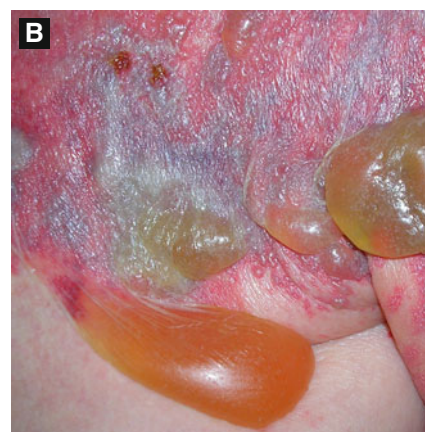
### Bullous Pemphigoid (BP) (Figure 3.26A–C)

- Most common autoimmune bullous disorder with chronic nature; typically in patients over 60
- **Autoantigen:**
  - **BPAG2** (collagen XVII): 180 kDa (NC16A domain), transmembrane hemidesmosomal protein
  - **BPAG1:** 230 kDa, cytoplasmic plaque protein
- **Clinical:** often presents with initial urticarial lesions which evolve into large, tense bullae over medial thighs, groin, abdomen, and legs;  $\pm$  pruritus initially with subsequent tenderness; no constitutional symptoms unless extensive disease; 10–35% with oral involvement
- **Drug-induced:** furosemide, NSAIDs, phenactin, PCN-derivates, gold, potassium iodide, captopril, enalapril, D-penicillamine, sulfasalazine

Drug-induced: **PF ChaNGS** Penicillamine PCN-derivates Phototherapy  
Furosemide Captopril NSAID Gold Sulfasalazine

- **Histology:** subepidermal bulla with  $\uparrow\uparrow$  eosinophils and lymphocytes in papillary dermis,  $\pm$  neutrophils
- **DIF:** linear C3 and IgG (latter weaker) at BMZ
- **IIF:** + in 60–80%; IIF on salt-split skin (SSS) shows binding to epidermal side of split (roof of blister)
- **Treatment:** oral corticosteroid, steroid-sparing agent (azathioprine, mycophenolate mofetil, etc.), TCN + nicotinamide, dapsone; good prognosis

**Anti-p105 pemphigoid** (105 kDa) } Similar to BP but autoantibodies targeting  
**Anti-p200 pemphigoid** (200 kDa) } distinct antigens of epidermal BMZ



**Figure 3.26**

**A: Bullous pemphigoid**

(Courtesy of Dr. Paul Getz)

**B: Bullous pemphigoid**

(Courtesy of Dr. Iris K. Aronson)

**C: Bullous pemphigoid**

(Courtesy of Dr. Iris K. Aronson)

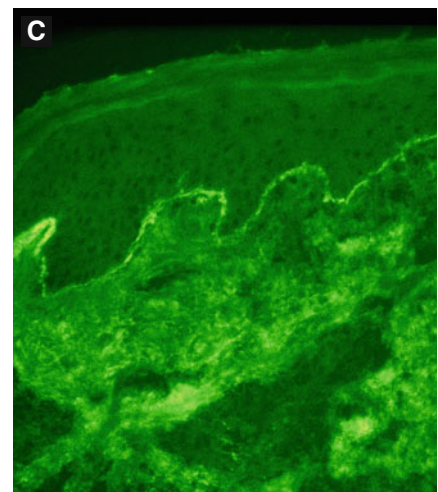


**Cicatricial Pemphigoid** (Figure 3.27A, B)

- Rare autoimmune disease involving the mucous membrane with subsequent scarring
  - **Autoantigen:**
    - BPAG2 (collagen XVII): mucosa and skin
    - $\beta$ 4 subunit of  $\alpha$ 6 $\beta$ 4 transmembrane hemidesmosomal protein (pure ocular)
    - Laminin 5 (aka epiligrin):  $\uparrow$  risk cancer
- Anti-epiligrin CP binds **DERMAL** side
- **Clinical:** ocular symptoms (conjunctivitis, burning or foreign body sensation), entropion, trichiasis with subsequent corneal irritation, corneal neovascularization, scarring, fusion of palpebral and bulbar conjunctivae, symblepharon, and blindness; may also involve mouth (erosions, ulcers, desquamative gingivitis), oropharynx, nasopharyngeal, esophageal, rectal and genital mucosa; skin lesions in 25% cases
  - **Drug-induced** (similar to BP): thiol-containing (captopril, gold thiosulfate, D-penicillamine), NSAIDs (indomethacin), topical glaucoma solutions,  $\beta$ -blockers (practolol), clonidine, sulfadoxine
  - **Histology/DIF:** similar to BP
  - **IIF:** + in 20% cases; IIF on (SSS) shows binding to epidermal side of split (roof), however, anti-laminin 5 CP binds to dermal side
  - **Treatment:** dapsone first line for oral with cutaneous disease, topical/intralesional/oral corticosteroid, cyclophosphamide, azathioprine

**Linear IgA Bullous Dermatitis (LABD)** (Figure 3.27C)

- Rare, subepidermal blistering disease with IgA deposition at BMZ; likely identical to chronic bullous disease of childhood (CBDC)
- **Autoantigen:** LAD-1 (120 kDa, part of BPAG2); LAD-1 cleavage results in second autoantigen, LABD97 (97 kDa)
- **Clinical:** annular or grouped vesicles/bullae over extensor extremities and buttock typically in herpetetic arrangement; mucosal involvement
- **Drug-induced:** vancomycin (most common), captopril, cephalosporin, PCN, NSAIDs, phenytoin, sulfonamide
- **Histology:** subepidermal bullae with rich neutrophilic infiltrate in papillary dermis (may resemble DH)
- **DIF:** linear IgA ( $\pm$  C3) deposition at BMZ
- **IIF:** + in 60% cases, IIF on (SSS) shows binding to epidermal side of split (roof)
- **Treatment:** dapsone or sulfapyridine, low dose oral corticosteroid

**Figure 3.27****A: Cicatricial pemphigoid**

(Courtesy of Dr. Iris K. Aronson)

**B: Cicatricial pemphigoid**

(Courtesy of Dr. Iris K. Aronson)

**C: LABD, DIF**

(Courtesy of Dr. Lawrence Chan)

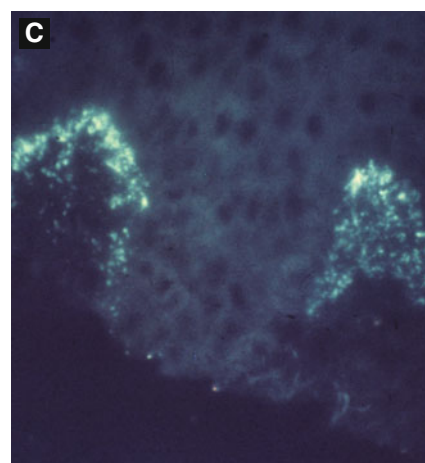
**Epidermal Bullous Acquisita (EBA)** (Figure 3.28A)

- Rare, acquired subepidermal blistering disease
- **Autoantigen:** type VII collagen
- **Clinical:** noninflammatory bullae with fragile skin in traumatized areas (hands, elbows, knees, toes); heals with atrophic scarring;  $\pm$  mucous membrane involvement
- **Histology:** subepidermal cleavage without acantholysis, variable amount of inflammatory infiltrate
- **DIF:** linear IgG ( $\pm$  C3, fibrinogen, IgA, IgM) at BMZ
- **IIF:** + in 50%; IIF on SSS shows binding to dermal side of split (floor)
- **Treatment:** generally unsatisfactory response

**Dermatitis Herpetiformis (Duhring's Disease)** (Figure 3.28B, C)

- Recurrent chronic pruritic disease associated with gluten-sensitive enteropathy
- Gluten: general name for storage proteins found in wheat, rye, and barley
  - NOT found in rice, oats or corn
  - Gliadin: soluble fraction; likely antigenic component
- **Autoantigen:** epidermal transglutaminase (TG-3), tissue transglutaminase (endomysial)
- **Clinical:** erythematous grouped papules or vesicles over elbows, knees, buttocks; intensely pruritic, so primary lesions typically not visible due to excoriations
- **Histology:** neutrophilic microabscesses in dermal papillae,  $\pm$  subepidermal vesicles
- **DIF:** granular IgA  $>$  C3 deposition in dermal papillae
- **IIF:** negative
- **Labs:** anti-gliadin/anti-endomysial antibodies in DH/celiac disease
- **Treatment:** dapsone (immediate skin improvement), referral to GI ( $>90\%$  with gluten-sensitive enteropathy and  $\uparrow$  risk of small bowel lymphoma)
- $\uparrow$  Incidence thyroid disease (Hashimoto's thyroiditis), IDDM, enteropathy-associated T cell lymphoma

Associated with **HLA-DQ2** (strongest), HLA-B8

**Figure 3.28**

**A:** Epidermolysis bullosa acquisita (EBA)\*

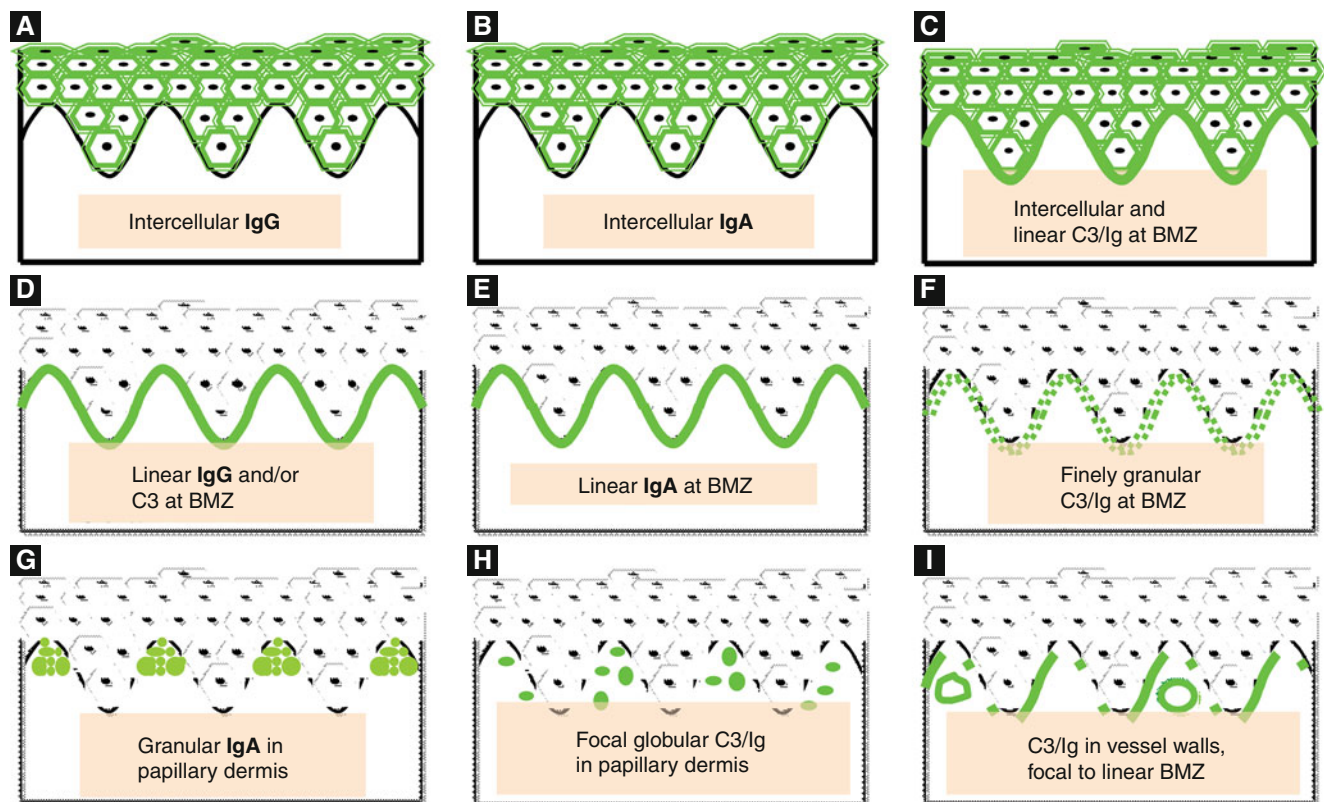
**B:** Dermatitis herpetiformis\*

**C:** Dermatitis herpetiformis, DIF\*

\*Courtesy of Dr. Paul Getz

**Table 3-17 Subepidermal Blistering Diseases**

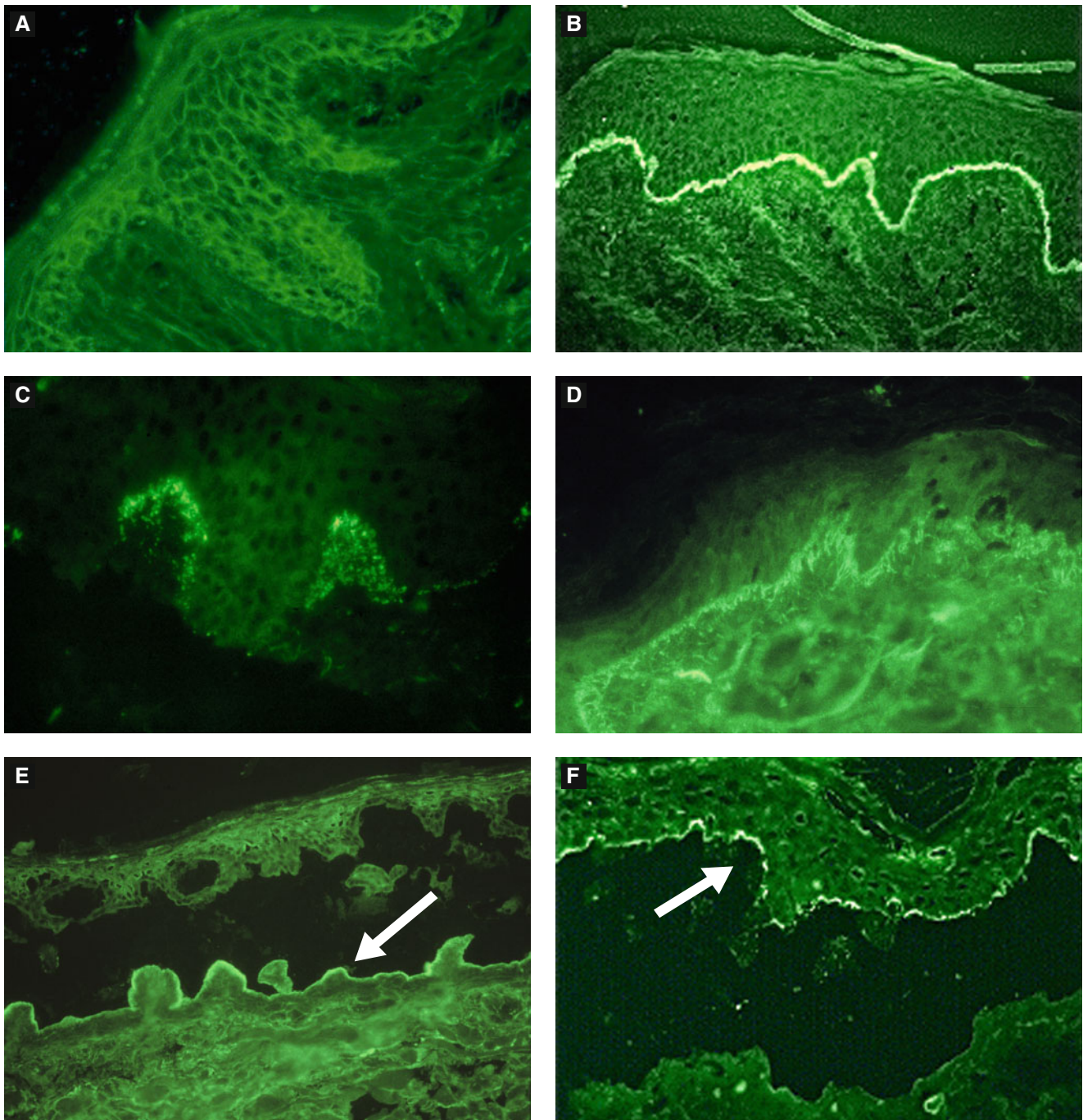
Disease	Antigen	DIF	IIF on SSS
<b>Bullous Pemphigoid</b>	BPAG2, BPAG1	Linear IgG/C3 at BMZ	Epidermal side
<b>Cicatricial Pemphigoid</b>	BPAG2, $\beta 4$ subunit, laminin 5 (epiligrin or laminin 332)	Linear IgG/C3 at BMZ	Epidermal side Anti-epiligrin CP binds <b>DERMAL</b> side
<b>Linear IgA Dermatitis</b>	97 kDa (LABD97) 120 kDa (LAD-1)	Linear IgA at BMZ	Epidermal side
<b>LP Pemphigoides</b>	BPAG2	Linear IgG/C3 at BMZ	Epidermal side
<b>Pemphigoid Gestationis</b>	BPAG2	Linear C3 at BMZ	Negative
<b>Epidermal Bullosa Acquisita</b>	Type VII collagen	Linear IgG at BMZ	Dermal side
<b>Bullous Lupus Erythematosus</b>	Type VII collagen	Linear IgG, IgM, IgA, C3 at BMZ	Dermal
<b>Porphyria Cutanea Tarda</b>		Linear IgG, IgM, IgA, C3 at BMZ and perivascular	Negative

**Figure 3.29**

A: Pemphigus vulgaris  
 B: IgA pemphigus  
 C: Paraneoplastic pemphigus  
 D: Bullous pemphigoid

E: Linear IgA bullous dermatosis  
 F: Lupus erythematosus  
 G: Dermatitis herpetiformis  
 H: Lichen planus  
 I: Porphyria cutanea tarda





**Figure 3.30**

**A: DIF, pemphigus vulgaris**

(Courtesy of Dr. Iris K. Aronson)

**B: DIF, bullous pemphigoid**

(Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases*, New York, NY: Springer; 2008)

**C: DIF, dermatitis herpetiformis**

(Courtesy of Dr. Paul Getz)

**D: DIF, lupus erythematosus**

(Courtesy of Dr. Paul Getz)

**E: IIF on SSS, EBA (dermal side)**

(Courtesy of Dr. Lawrence Chan)

**F: IIF on SSS, bullous pemphigoid (epidermal side)**

(Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases*. New York, NY: Springer; 2008)



**Friction Bulla**

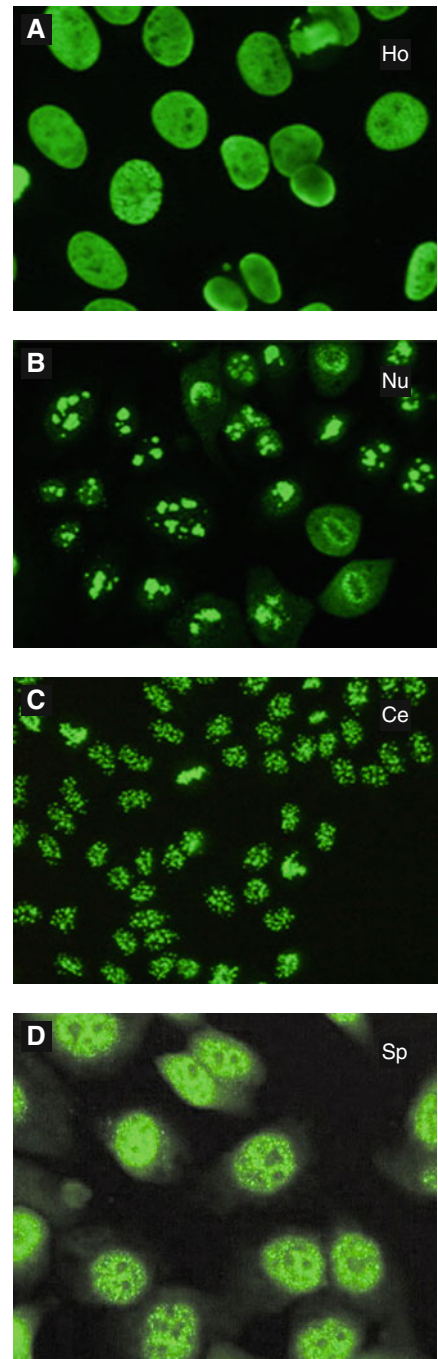
- Typically over heels and soles due to repeated friction
- Histology: intraepidermal blister from necrosis of keratinocytes with split below granular layer, sparse perivascular inflammatory infiltrate in superficial dermis
- Treatment: spontaneous healing

**Coma Bulla**

- Tense blisters forming on pressure sites of normal-appearing skin typically 48–72 h later; associated with loss of consciousness
- Histology: subepidermal split, ± epidermal necrosis, sweat gland necrosis, sparse inflammatory cell infiltrate
- Treatment: remove pressure at site, heals spontaneously

**3.6 CONNECTIVE TISSUE DISEASES****A. AUTOIMMUNE SEROLOGY (Table 3-18)****Antinuclear Antibody (ANA) (Figure 3.31A–D)**

- Family of autoantibodies which may be directed at one or several of the following nuclear antigens:
  - **Extractable nuclear antigens (ENAs)**
    - Sm (Smith)
    - RNP (U1 ribonucleoprotein)
    - Ro (SSA)
    - La (SSB)
    - Scl-70
    - Jo-1
  - **Non-ENAs**
    - ds-DNA (double stranded)
    - Histone
    - Nuclear RNA
- ANA assay measures the amount (titer) and pattern of antibodies in a patient's serum that bind autoantigens present in the nucleus of cells
- The titer represents the last doubling dilution in order to produce a sample with no fluorescence (ANA-free)
- Two types of assays: indirect IF (IIF) and ELISA
  - IIF: most accurate, uses Hep-2 epithelial carcinoma cells as substrate (due to ↑ nuclear/cytoplasmic ratio)
  - ELISA: more popular due to decreased cost
- Patterns of nuclear fluorescence if ANA titer positive:
  - Homogenous (diffuse) suggests anti-dsDNA (SLE)
  - Peripheral (rim) suggests anti-dsDNA (SLE)
  - Speckled suggests anti-U1RNP (MCTD, Sjögren)
  - Centromeric stains kinetochore (CREST)
  - Nucleolar suggests anti-fibrillarin (SSc)
- Five percent of normal population with elevated ANA but nonsignificant; ANA increases with age (i.e. 15% patients >55 years of age with ↑ ANA titer but no clinical significance)

**Figure 3.31****ANA patterns****A: Homogenous\*****B: Nucleolar\*****C: Centromeric\***

\*Reprint from Cuenca S, et al. Rationelle und rationale Laboratorium diagnostik in der Hals-Nasen-Ohren-Heilkunde. HNO. 2008; 56 (9); 855–73

**D: Speckled**

(Reprint from Vergani D, et al. Autoimmune Hepatitis. Seminars in Immunopathology. 2009; 31 (3); 421–435)

Table 3-18 Autoimmune Antibodies

Antibody	Antigen	Prevalence	Clinical Associations
<b>Systemic Lupus Erythematosus (SLE)</b>			
<b>Anti-dsDNA</b>	Native DNA	40–90%	Highly specific, <b>lupus nephritis</b> , correlates with <b>disease activity</b> , <b>early/severe</b> disease
<b>Anti-Sm</b>	Ribonucleoprotein	10–30%	Highly specific, <b>lupus nephritis</b>
<b>Anti-rRNP</b>	Ribosomal P protein	10%	Highly specific, <b>neuropsychiatric LE</b>
<b>Anti-Ro (SSA)</b>	Ribonucleoprotein	40–60%	Mild SLE, <b>photosensitivity</b> , <b>SCLE</b> , <b>neonatal LE/congenital heart block</b>
<b>Anti-La (SSB)</b>	Ribonucleoprotein	20–30%	Same as anti-Ro associations
<b>Anti-U1RNP</b>	Ribonucleoprotein	30–60%	SCLE, mild SLE with limited systemic involvement
<b>Anti-histone</b>	Histone	40%	<b>Drug-induced</b> ← SLE mainly but can also be seen in SCLE
<b>Anti-Ku</b>	p70/p80 nucleolar protein (DNA repair)	10%	SLE with <b>polymyositis</b>
<b>Anti-ssDNA</b>	Denatured DNA	70%	Possible risk for SLE in DLE patients
<b>Anti-C1q</b>	C1q of complement	60%	Severe SLE, lupus nephritis
<b>Anti-cardiolipin</b>	Cardiolipin (phospholipid)	50%	Increased risk of <b>thrombotic events</b> , recurrent fetal loss, thrombocytopenia
<b>Sjögren Syndrome</b>			
<b>Anti-α-fodrin</b>	Actin-binding ptn	70%	
<b>Anti-Ro</b>	Ribonucleoprotein	60%	↑ Risk of <b>systemic disease</b> and <b>lymphoma</b>
<b>Anti-La</b>	Ribonucleoprotein	35–85%	Same as anti-Ro
<b>Systemic Sclerosis</b>			
<b>Anti-Scl-70</b>	DNA topoisomerase I	25%	Diffuse skin disease, interstitial lung disease
<b>Anti-RNA polymerase III</b>	RNA polymerase III	20%	Rapid-onset and <b>severe</b> disease with major organ and <b>diffuse cutaneous</b> involvement
<b>Anti-fibrillarin</b>	<b>U3RNP</b>		Diffuse skin disease, <b>pulmonary HTN</b>
<b>Anti-centromere</b>	5–30%		<b>CREST</b>
<b>Anti-Ku</b>	p70/p80 nucleolar protein (DNA repair)	10%	
<b>Dermatomyositis</b>			
<b>Anti-155 kDa and anti-Se</b>	Uncharacterized nuclear proteins	80%	<b>Amyopathic</b> dermatomyositis, <b>cancer-associated</b> dermatomyositis
<b>Anti-Jo1</b>	Histidyl tRNA synthetase	20%	<b>Antisynthetase syndrome</b> : Raynaud's phenomenon, mechanic's hands, pulmonary fibrosis, arthritis, myositis
<b>Anti-SRP</b>	Signal recognition particle	5%	<b>Cardiac</b> involvement, severe DM/PM, poor prognosis
<b>Anti-Mi2</b>	Nuclear helicase	15%	Hallmark <b>skin lesions</b> , <b>good prognosis</b>
<b>Anti-Ku</b>	p70/p80 protein	<5%	DM/PM overlap with SLE or scleroderma
<b>Anti-PM/Scl</b>	Nucleolar proteins	<10%	DM/PM overlapping with <b>scleroderma</b>
<b>PL-7, PL-12</b>	tRNA synthetase	3%	<b>Antisynthetase syndrome</b>
<b>Mixed Connective Tissue Disease (MCTD)</b>			
<b>Anti-U1RNP</b>	Ribonucleoprotein	100%	

## B. CONNECTIVE TISSUE DISEASES

### ***Lupus Erythematosus (LE)***

- Spectrum with three major forms: systemic LE (SLE), subacute LE (SCLE) and chronic cutaneous LE (CCLE)
- **Chronic cutaneous LE (discoid LE)** (Figure 3.32A–C)
  - Chronic cutaneous form with involvement typically of face/scalp in young women; ↑ incidence in African American patients
  - Presents with indurated erythematous thin papules with adherent scale and follicular plugging on face, scalp and/or ears (concha bowl), ‘carpet tack’ sign (follicular plugs with removal of scale); subsequent atrophy, telangiectasias, dyschromia, scarring (SCC may develop in scars); ¼ with oral involvement; no systemic symptoms or extracutaneous involvement; rarely may see widespread discoid involvement (↑ serologic abnormalities have ↑ likelihood to develop SLE)
  - Variants
    - **Tumid lupus:** deeper, more nodular lesions with erythema and induration mainly involving face and trunk, no scaling or follicular plugging; dermis with mucin and intense inflammatory infiltrate
    - **Lupus panniculitis or profundus:** tender subcutaneous nodules with typical DLE surface changes involving buttocks, chest, shoulder, face; heals with deep atrophy; 10–15% meet SLE criteria
    - **Hypertrophic or verrucous LE:** hyperkeratotic or verrucous papules/plaques over extensor arms, ± face/trunk, may appear similar to warts
    - **Chillblain LE:** acral dusky purple papules and plaques associated with acrocyanosis, minimal atrophy/scarring
  - Histology: atrophic epidermis with plugged follicles, vacuolar degeneration of basal layer, thickened basement membrane, melanin incontinence, perivascular/periadnexal lymphocytic infiltrate, ↑ mucin between collagen bundles; 90% of lesional biopsies show diffuse irregular band of IgG/C3 at BMZ (lupus band)
  - Labs: ¼ with + ANA (low titer); 5–10% with DLE may develop SLE over time
  - Treatment: sun avoidance, topical/IL corticosteroid, oral antimalarial, topical calcineurin inhibitor

Of note, C2 deficiency increases susceptibility to autoimmune conditions, especially lupus (DLE, SCLE, SLE)



**Figure 3.32**

**A: Discoid LE\***

**B: Discoid LE\***

**C: Discoid LE\***

\*Courtesy of Dr. Paul Getz



- **Subacute cutaneous LE (SCLE)** (Figure 3.33A, B)
  - Overlap between DLE and SLE with photosensitivity
  - Presents with papulosquamous or annular/polycyclic erythematous scaly patches/plaques on shoulders, trunk, extensor arms; face typically spared; heal without scarring but telangiectasias common; fatigue and arthralgias common but limited organ involvement
  - Histology: atrophic epidermis, some vacuolar change of BMZ, sparse inflammatory infiltrate
  - Labs: 60–80% with + ANA, anti-Ro (60–90%)
  - Course: persistent with intermittent flares, up to 50% will eventually meet SLE criteria (but milder disease)
  - Treatment: sun protection, antimalarial, oral corticosteroid, dapsone or other immunosuppressive agent (topical corticosteroids rarely sufficient alone)
  - Associations: HLA-B8 (strongest), HLA-DR3, HLA-DRw52, HLA-DQ1

Drug-induced SCLE: **hydrochlorothiazide, terbinafine, diltiazem, ACEI, NSAIDs, griseofulvin, antihistamines, IFN, PUVA, TNF $\alpha$**



- **Systemic LE (SLE)** (Figure 3.33C)
  - Systemic multi-organ involvement typically in young adults; ↑ incidence in African American patients
  - Need 4 out of 11 criteria for diagnosis (see below)
  - Cutaneous lesions include bilateral malar erythema following sun exposure, discoid lesions, oral ulcerations, photosensitivity, patchy to diffuse nonscarring alopecia with lupus hairs (along frontal scalp line), Raynaud's phenomenon, livedo reticularis, acrocyanosis, cutaneous signs of antiphospholipid syndrome, urticarial vasculitis, red lunulae, multiple dermatofibromas
  - Histology: modest vacuolar change, perivascular and periadnexal lymphocytic infiltrate, ↑ dermal mucin
  - Labs: >95% with + ANA, anti-dsDNA and anti-Sm are both highly specific for SLE, see Table 3.18 for details
  - Treatment: antimalarial, oral/topical corticosteroid, steroid-sparing immunosuppressive agent
  - Associations: HLA-DR2, HLA-DR3

Drug-induced SLE: **hydralazine, procainamide, chlorpromazine, INH, quinidine, practolol, d-penicillamine, PUVA, minocycline**



- Criteria (need 4 out of 11):

Malar erythema	Discoid LE	+ ANA	Arthritis
Hematologic disorder	Immunologic (dsDNA, Sm)	Neurologic disorder	Serositis
Photosensitivity	Nephropathy	Oral ulcers	

**MD SOAP BRAIN:** Malar rash, Discoid rash, Serositis, Oral ulcers, Arthritis, Photosensitivity, Blood (heme), Renal, ANA, Immuno abnormality, Neurologic



**Figure 3.33**  
**A: SCLE\***  
**B: SCLE\***  
**C: SLE, malar erythema\***  
*\*Courtesy of Dr. Iris K. Aronson*



**Dermatomyositis (DM)** (Figure 3.34A–C)

- Chronic inflammatory dermatomyopathy presumed to be from immune-mediated process with bimodal peak; may only involve skin (amyopathic DM or DM sine myositis) or only muscle (polymyositis); skin findings typically occur 2–3 months before muscle weakness
- Presents with facial erythema, violaceous poikiloderma of eyelids with edema (heliotrope sign), violaceous papules over MP joints (Gottron's papules), reddish scaling over knuckles, knees and elbows (Gottron's sign), ragged cuticles (Samitz sign), nailfold telangiectasias, photodistributed poikiloderma (violaceous),  $\pm$  hyperkeratosis and fissuring of hands (mechanic's hands),  $\pm$  calcinosis (seen more in juvenile DM),  $\pm$  fever, malaise; proximal symmetric muscle weakness (inability to comb hair, inability to rise from seated position or climb stairs)
  - Sclerodermoid changes associated with anti-Ku
  - Antisynthetase syndrome (pulmonary disease, arthritis, Raynaud's, myositis) seen with anti-tRNA synthetase antibodies (anti-Jo-1, anti-PL7, anti-PL12)
  - Cardiac involvement and poor prognosis seen with anti-SRP antibodies
- Associations: lung and GI cancer most common in men; ovarian and breast cancer in women
- Histology: epidermal atrophy, vacuolar change, mucin deposition, lymphocytic infiltration (similar to LE), dermal sclerosis in older lesions; muscle biopsy (deltoid frequently) or MRI
- Labs: ANA (60%); muscle enzymes:  $\uparrow$  creatine kinase (CK, 90%) and aldolase;  $\uparrow$  ESR,  $\uparrow$  transaminases,  $\uparrow$  LDH
- Treatment: oral corticosteroid (followed by taper) + steroid-sparing agent, antimalarial, sun protection

CK most sensitive enzyme, but not specific for inflammatory myopathies

**Mixed Connective Tissue Disease (MCTD)**

- Clinical overlap with systemic sclerosis and DM with specific serology (U1RNP) and clinical findings
- Presents with Raynaud's phenomenon, dactylitis ('sausage digits'), acrosclerosis, arthritis, low-grade fever; skin findings include sclerodermoid or poikilodermatous change of upper trunk;  $\pm$  esophageal dysmotility, pulmonary hypertension
- Histology: may resemble LE or may show vasculitis
- Labs: hallmark is U1RNP antibody and characteristic speckled pattern on immunofluorescence
- Treatment: oral corticosteroid, steroid-sparing agent, topical steroids

Associated with HLA-DR4 and HLA-DR2



**Figure 3.34**

**A: Gottron's papules (DM)\***

**B: Poikiloderma (DM)\***

**C: Calcinosis cutis (DM)\***

*\*Courtesy of Dr. Iris K. Aronson*

### Sjögren Syndrome (Sicca Syndrome, Mikulicz Disease)

- Chronic autoimmune disorder affecting exocrine gland function with xerophthalmia (dry eyes or keratoconjunctivitis sicca), xerostomia (dry mouth) and arthritis
- May be primary disorder or associated with other autoimmune diseases such as SLE
- Antibodies: anti- $\alpha$ -fodrin (70%), anti-Ro and anti-La
- Presents with xerosis of the mucous membranes (mouth, eyes, vagina) and skin (pruritus), fatigue and arthritis; xerophthalmia with foreign body sensation, positive Schirmer test (detects  $\downarrow$  lacrimal gland secretion: paper wick placed over lower eyelid for 5 min, abnormal with typically  $<5$  mm of moistening) and subsequent corneal ulceration and keratitis;  $\pm$  vasculitis, renal involvement, parotid gland enlargement, peripheral neuropathy, lymphadenopathy with  $\uparrow$  risk of lymphoma
- Labs:  $\uparrow$  ESR, + rheumatoid factor, + anti-fodrin, + anti-Ro, + anti-La; leukopenia
- Histology: dense lymphocytic infiltrate surrounding minor salivary glands (need presence of two or more aggregates for diagnosis)
- Treatment: mainly supportive; artificial tears, cyclosporine eye drops, methylcellulose drops (artificial saliva), sugarless water, etc.; immunosuppressants for patients with vasculitis or internal organ involvement
- Associated with HLA-B8, HLA-DR3, HLA-DQ2, HLA-DRw52

### Scleroderma

- Group of autoimmune disorders with initial inflammation and subsequent sclerosis; unknown etiology
- **Morphea (localized scleroderma)** (Figure 3.35A–C)
  - Localized form of scleroderma with unknown etiology, possibly due to trauma or infection (i.e. *Borrelia burgdorferi*)
  - Presents initially with expanding erythema  $\rightarrow$  turns into ivory-colored sclerotic plaque  $\rightarrow$  eventually softens; typically becomes inactive within 3–5 years
  - Variants: disseminated morphea, guttate morphea, linear morphea (linear scleroderma), nodular morphea, morphea profunda, progressive hemifacial atrophy (Parry Romberg syndrome)
  - Histology: dense lymphocytic infiltrate around superficial/deep vessels with few eosinophils, inflammation between dermal-subcutaneous fat junction; advanced lesions with dermal sclerosis
  - Labs:  $\pm$  ANA in disseminated or linear morphea (unlikely to see with plaque-type morphea)
  - Treatment: topical mid to high potency corticosteroid, topical vitamin D analogue, PUVA or UVA1



**Figure 3.35**

**A: Morphea**

(Courtesy of Dr. Paul Getz)

**B: Morphea**

(Courtesy of Dr. Sophie M. Worobec)

**C: Morphea**



- **Systemic Sclerosis (SSc)** (Figure 3.36A–C)
  - Systemic disorder affecting the skin, blood vessels and internal organs; early events in pathogenesis include vascular dysfunction and endothelial injury; fibrosis related to TGF- $\beta$ , endothelin-1, PDGF, and connective tissue growth factor (CTGF)
  - Onset typically in women (30–50 years/old); African American patients with earlier onset and  $\uparrow$  risk of diffuse disease
  - Presents with varying symptoms:
    - **Cutaneous:** pruritus, initial edematous phase (pitting edema of digits) with subsequent sclerosis (shiny, taut appearance) and digital ulcerations, sclerosis may affect arms, face (mask-like) and/or neck; dyspigmentation with leukoderma sparing perifollicular skin ('salt/pepper' sign) or diffuse hyperpigmentation; calcinosis cutis
    - **Vascular:** Raynaud's phenomenon (vasospasm of digital arteries secondary to cold stimulus with classic color change: white  $\rightarrow$  blue  $\rightarrow$  red)
    - **Other:** symmetric synovitis, migratory polyarthritis, pulmonary (interstitial lung disease  $\rightarrow$  pulmonary fibrosis), cardiac, renal, GI (reflux, dysphagia)
  - Labs: ANA (nucleolar/centromeric), anti-Scl-70, anti-fibrillarin, anti-centromere, anti-RNA polymerase
  - Histology: normal to atrophic epidermis, hyalinized dermis with  $\uparrow$  collagen deposition,  $\downarrow$  adnexal structures, loss of subcutaneous fat
  - Treatment:
    - Raynaud's: cold temperature avoidance, calcium channel blockers (nifedipine), low dose aspirin, prostaglandin E1
    - Cutaneous ulcers: oral endothelin receptor antagonist (i.e. bosentan) may prevent new ulcers
    - Systemic: prostaglandins (prostaglyclin), immunosuppressants, D-penicillamine, ACEI

Systemic sclerosis:  $\uparrow$  expression of extracellular matrix (ECM) proteins from dermal fibroblasts and  $\uparrow$  deposition of **collagen type III**

- **CREST (limited SSc)** (Figure 3.37A)
  - Limited form of systemic sclerosis
  - CREST: calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasias
  - Associated with anti-centromere antibodies, rarely progresses to SSc, better prognosis than SSc



**Figure 3.36**

**A: Systemic sclerosis\***

**B: Systemic sclerosis\***

**C: Systemic sclerosis\***

*\*Courtesy of Dr. Paul Getz*

**Nephrogenic Systemic Sclerosis (Nephrogenic Fibrosing Dermopathy)**

- Seen in patients with ESRD; associated with exposure to gadolinium-based contrast medium
- Indurated fibrotic plaques on extremities and trunk with brawny hyperpigmentation,  $\pm$  joint contractures
- Histology: dermal sclerosis with  $\uparrow$  # of CD34+ cells
- Treatment: UVA1, restoration of renal function

**Relapsing Polychondritis (Figure 3.37B)**

- Episodic inflammatory condition involving cartilaginous structures (ear) with suspected autoimmune origin
- Antibodies: anti-type II collagen (<50%),  $\pm$  anti-matrilin-1 (cartilage extracellular matrix protein)
- Presents with episodes of painful, beefy red erythema and edema of cartilaginous portion of ears (earlobes spared); over time cartilage destroyed ('cauliflower' or floppy ears); nasal chondritis (saddle nose deformity), respiratory tract involvement (hoarseness), migratory arthralgia,  $\downarrow$  hearing (deafness, tinnitus), ocular symptoms
- Histology: perichondrial inflammation with neutrophils, plasma cells or lymphocytes, cartilage degeneration ( $\downarrow$  basophilia, vacuolization of chondrocytes); advanced lesions with perichondrial fibrosis
- Treatment: oral corticosteroids, dapsone, other immunosuppressants (MTX, azathioprine, etc.)
- Associated with myelodysplastic syndrome, Behcet's disease (MAGIC syndrome)
- Association: HLA-DR4

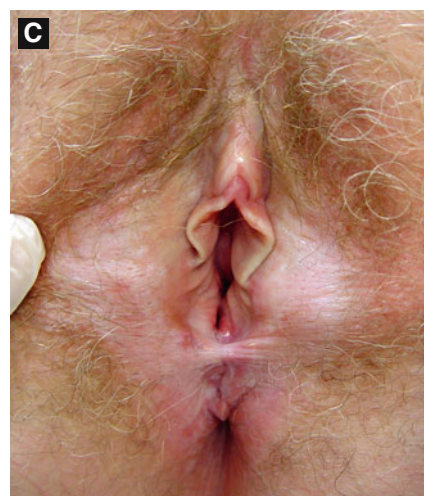
**Magic Syndrome**

- Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome; antibodies to type II collagen, treatment similar to relapsing polychondritis

**C. OTHER CONNECTIVE TISSUE DISEASES****Lichen Sclerosus (LSetA) (Figure 3.37C)**

- Autoimmune disease occurring in children and women in the 5th or 6th decade (less often in men)
- Autoantibody likely to extracellular matrix protein-1 (ECM-1)
- Presents initially as pruritic hypopigmented plaques typically with pink inflammatory border most commonly in genital area; expands and becomes atrophic,  $\pm$  follicular hyperkeratosis; figure-of-eight pattern if perianal/vulvar area involved; dyspareunia, difficulty urinating, scarring/contractures (if advanced),  $\uparrow$  risk of SCC in sclerotic areas
- Histology: atrophic epidermis,  $\pm$  follicular plugging, vacuolar degeneration at basal layer, band-like lymphocytic infiltrate, pale staining homogenized collagen with edema ( $\pm$  subepidermal bulla), dilated lymphatic vessels
- Treatment: superpotent topical corticosteroid
- Associated with other autoimmune diseases (i.e. thyroid disease, pernicious anemia)

Five percent lifetime risk of SCC

**Figure 3.37****A: Telangiectasias in CREST***(Courtesy of Dr. Paul Getz)***B: Relapsing polychondritis***(Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007)***C: Lichen sclerosus***(Courtesy of Dr. Iris K. Aronson)*



**Perforating Disorders** (Figure 3.38)

- Group of disorders characterized by transepidermal elimination of altered dermal connective tissue or keratin
- See Table 3-19



**Figure 3.38**  
**Acquired perforating dermatosis**  
*(Courtesy of Dr. Paul Getz)*

**Table 3-19 Perforating Disorders**

Disease	Description	Histology	Associations
<b>Acquired perforating dermatosis</b> (Kyrle's disease) (Acquired reactive perforating collagenosis)	Intensely pruritic umbilicated papules with keratinous plugs involving extensor limbs, less common on trunk/face, + Köebner phenomenon	Cup-shaped invagination of epidermis with hyperkeratotic plug containing inflammatory debris and collagen fibers, vertically oriented collagen extruded into plug (in dermis)	Diabetes or renal failure (many patients on hemodialysis), some cases related to malignancy
<b>Inherited reactive perforating collagenosis</b>	Similar lesions but occur in childhood	Similar histology to acquired form	None
<b>Elastosis perforans serpiginosa (EPS)</b>	Skin-colored to red papules in serpiginous, linear or arciform pattern over upper extremities or neck, may measure several centimeters in diameter	↑↑ Amount of <u>elastic fibers</u> in papillary dermis appearing clumped and 'clutched' by epidermis (hyperplastic); elastic fibers and inflammatory cells extruded via granulomatous reaction	Associated with:  <b>MADD PORES:</b> Marfan's, Acrogeria, Down syndrome, D-Penicillamine, Pseudoxanthoma elasticum, Osteogenesis imperfecta, Rothmund-Thomson, Ehlers Danlos, Scleroderma
<b>Perforating folliculitis</b>	Keratotic follicular papules commonly over extensor surfaces	Involved hair follicle shows disruption of lateral wall; parakeratotic plug consists of collagen, elastic fibers and inflammatory cells	Chronic renal failure and diabetes
<b>Perforating periumbilical calcific elastosis</b>	Keratotic papules involving the abdomen	Transepidermal elimination of calcified elastic fibers	African-American women, multiparity

### 3.7 DISORDERS OF FAT (Tables 3-20, 3-21, 3-22)

**Table 3-20 Disorders of Fat**

Disease	Clinical Findings	Pathology	Associations
<b>Anetoderma</b>	Focal dermal defect: localized areas of atrophic skin with laxity or herniated appearance over trunk, thighs and arms, ± overlying skin depressed or macular	Normal epidermis, ↓ or <u>absent</u> elastic tissue in dermis with special stain (may appear normal on H&E), ± perivascular lymphocytes	May be primary (idiopathic) or secondary (infection, inflammatory cutaneous disorder or tumor)
<b>Atrophoderma of Pasini and Pierini</b>	Single to multiple well-demarcated oval hyperpigmented patches with slight depression on back (most common) in young adults and adolescents  If linear following Blaschko's lines → atrophoderma of Moulin	Minimal change including flattening of rete ridges, basal layer with ↑ melanin, ↓ dermal thickness, ± perivascular infiltrate	Unclear if atypical atrophic form of morphea or separate entity; may be related to <i>B. burgdorferi</i>
<b>Mid-dermal elastolysis</b>	Areas with diffuse fine wrinkling over trunk, upper arms and/or neck, ± preceding erythema	Normal epidermis, selective loss of elastic fibers in mid dermis	None
<b>Follicular atrophoderma</b>	Dimple-like depression in follicular orifices consistent with ice-pick depressions on <u>dorsal hands/feet</u> or cheeks	Dilated pore ± with underlying atrophy, often ↓ elastic fibers  If limited to cheeks → atrophoderma vermiculatum (Rombo syndrome, Nicolau-Balus syndrome)	Bazex syndrome Conradi-Hünermann-Happle syndrome
<b>Piezogenic pedal papules</b>	Skin-colored papules in heels with pressure (due to herniation of fat), disappears when weight removed	Fragmentation of dermal elastic tissue and herniation of fat into dermis	Normal variant

**Table 3-21 Lipomatoses**

Disease	Clinical Findings
<b>Adiposis dolorosa</b> (Dercum's disease)	Multiple painful lipomas on trunk, arms, periarticular region typically in postmenopausal women; associated with depression and weakness
<b>Diffuse congenital lipomatosis</b>	Poorly demarcated lipomas infiltrating subcutaneous tissue, muscle and skin over lower extremities and trunk
<b>Familial multiple lipomatosis</b>	Multiple circumscribed lipomas in several members of a family, typically over forearms and thighs
<b>Benign symmetric lipomatosis</b> (Madelung's disease)	Diffuse infiltrative fat deposits in head, neck and shoulder girdle region, typically in men
<b>Gardner syndrome</b>	Multiple lipomas + polyposis of colon, epidermoid cysts, congenital hypertrophy retinal pigment epithelium, APC gene mutation

Table 3-22 Panniculitides

Disease	Clinical Findings	Pathology	Associations
<b>Erythema nodosum (EN)</b>  <b>Positive</b> prognostic factor in sarcoidosis and coccidioidomycosis  Do not confuse with erythema nodosum leprosum (vasculitis)	Delayed hypersensitivity response with painful, erythematous subcutaneous nodules commonly over pretibial areas → progress to bruise-like color, ± fever, arthralgias, malaise  Typically self-limited	<b>Septal</b> panniculitis; edematous widened septae with giant cells, neutrophils → later see lymphocytes, ± septal fibrosis, foamy histiocytes, Miescher's microgranulomas (clusters of histiocytes surrounding clefts)	<b>Idiopathic (30%), strep infection</b> (also viral, deep fungal), <b>sarcoidosis</b> , <b>drugs</b> (OCP, sulfonamides), <b>Behçet's</b> , malignancy  <b>IBD (Crohn's &gt; UC)</b> ↗  Per Bologna and Harrison  Treatment (dependent on etiology): bed rest, NSAID, colchicine, potassium iodide (KI)
<b>Subacute nodular migratory panniculitis (EN migrans)</b>	Nodules that migrate or expand centrifugally, often unilateral; chronic course	Chronic septal panniculitis with greater septal thickening than EN	Most idiopathic, ± associated strep infection or thyroid disease  Treatment: KI
<b>Morphea/scleroderma panniculitis</b>	Deep indurated plaques typically over extremities	Septal panniculitis with mucin, thickened septae, lymphocytes and plasma cells	Treatment: see section on morphea
<b>Erythema induratum (Bazin's disease)</b>  Unlike shin location of EN	Erythematous plaques or nodules commonly over <b>calves</b> , ± ulceration, drainage	Lobular or mixed panniculitis: mixed infiltrate (histiocytes, lymphocytes, giant cells, plasma cells), <b>vasculitis</b> often in fat, ± caseation necrosis, fibrosis later	Associated with <b>tuberculosis</b> ; if no TB association, termed 'nodular vasculitis'  Treat underlying TB
<b>α1-antitrypsin deficiency panniculitis</b>  α1-antitrypsin: major protease inhibitor in serum	Erythematous, tender subcutaneous nodules that often <b>ulcerate with oily discharge</b> ; commonly in lower trunk and extremities, ± fever, pleural effusion, pulmonary embolism	Lobular panniculitis with neutrophils and lymphocytes, <b>liquefactive necrosis of fat</b> (foamy macrophages, ± cystic spaces), 'skip areas' of normal fat next to necrotizing area	Deficiency of α1AT  May have associated chronic liver disease, <b>emphysema</b> , pancreatitis, angioedema, glomerulonephritis
<b>Pancreatic panniculitis (Pancreatic fat necrosis)</b>	Subcutaneous nodules often on legs (± trunk, arms, scalp), ± oily discharge; ± fever, abdominal pain, arthralgias, ascites	Septal panniculitis → lobular or mixed with <b>fat necrosis</b> and 'ghost-like' lipocytes, <b>basophilic calcium deposition</b> in fat	Pancreatitis and pancreatic carcinoma  Amylase levels peak 2–3 days after eruption
<b>Post-steroid panniculitis</b>	Firm, red plaques on cheeks, trunk and arms, ± associated pruritus or tenderness	Predominantly lobular panniculitis, <b>needle-shaped clefts</b> in lipocytes or giant cells	Occurs after rapid withdrawal of systemic corticosteroids
<b>Lupus panniculitis (Lupus profundus)</b>	Tender, subcutaneous plaques and nodules on face, upper outer arms, trunk, shoulders and hips, 'tethered' depressed appearance; chronic, relapsing nature	Lobular panniculitis: <b>hyaline necrosis</b> of fat lobules, ± mucin, 'lymphoid follicles' (aggregates of lymphocytes), ± LE epidermal changes, ± vasculitis	Typically occurs antecedent to other manifestations of LE, closer relationship to CCLE than SLE  Treatment: antimalarials often

**Table 3-22 Panniculitides (cont'd)**

Disease	Clinical Findings	Pathology	Associations
<b>Cold panniculitis</b> (Equestrian or popsicle panniculitis)	Erythematous, firm nodules or plaques typically over cheeks and chin (can be on outer thighs in equestrian panniculitis)	Lobular panniculitis with mixed infiltrate, perivascular dermal lymphocytic infiltrate with ↑↑ inflammation at dermal-subQ junction, + mucin, cystic spaces in fat	Usually infants and children exposed to cold (i.e. weather, cold food such as popsicle) Self-limited
<b>Sclerosing lipogranuloma</b> (Paraffinoma)	Pain and erythema with induration, ± ulceration with oily discharge, often involving the penis or scrotum	Granulomatous lobular panniculitis with ↑ fibrosis, many round vacuoles of varying sizes in dermis and subcutis (' <b>Swiss-cheese</b> ')	Usually due to self-injection of oily materials (paraffin or silicone) Treatment: excision if small
<b>Factitial panniculitis</b>	Inflamed nodules (etiology hinted by distribution of lesions)	Central nidus of subcutaneous inflammation	Typically self-inflicted by psychiatric patients
<b>Lipodermato-sclerosis</b> (Sclerosing panniculitis)	Wood-like induration, hyperpigmentation and erythema on lower legs bilaterally ('inverted wine bottle')	Thickening of dermis and septae, microcysts in lobules, cyst wall with PAS + cuticle-like <b>eosinophilic membrane</b> , pericapillary fibrin	Associated with chronic venous insufficiency Treatment: compression therapy, pentoxifylline, stanozolol
<b>Cytophagic histiocytic panniculitis</b>	Subcutaneous nodules ± ulceration on trunk/extremities; fulminant systemic disease with fever, liver failure, DIC, pancytopenia	Mixed panniculitis: macrophages (called 'bean bag' cells) contain erythrocytes, lymphocytes or karyorrhectic debris ( <b>cytophagocytosis</b> )	Most cases associated with T cell lymphoma (specifically subcutaneous panniculitis-like T cell lymphoma)



### 3.8 PREGNANCY DERMATOSES

#### Physiologic Pregnancy Changes

- Pigmentary
  - Melasma
  - Hyperpigmentation around areolae
  - Linea nigra on abdomen
  - Darkening of nevi
- Vascular
  - Spider angiomas
  - Palmar erythema
  - Varicosities
  - Non-pitting edema
  - Pyogenic granulomas
- Hair
  - Hypertrichosis (prolongation of anagen phase)
  - Postpartum telogen effluvium (synchronized transition into telogen phase)
  - Androgenetic alopecia
- Nail
  - Onycholysis
  - Brittleness
- Connective tissue
  - Striae

#### Pemphigoid Gestationis (Herpes Gestationis) (Figure 3.39A–C)

- Autoimmune bullous dermatosis of pregnancy; typically second or third trimester or immediately postpartum
- **Antibody:** anti-BPAG2 (BP180, NC16A site)
- Presents with pruritic urticarial papules on trunk (typically periumbilical), may progress to tense vesicles/bullae and spreads peripherally (spares mucous membranes, face, palms and soles);  $\pm$  flare with delivery (75%);  $\pm$  recurrence with OCPs, menses or subsequent pregnancy;  $\uparrow$  mother's risk for Graves' disease
- **Histology:** papillary dermal edema resulting in subepidermal bulla with eosinophil-rich infiltrate,  $\pm$  keratinocyte necrosis, perivascular infiltrate
- **DIF:** linear C3 deposition  $\pm$  IgG at basement membrane (key assay test to differentiate from PUPPP)
- **IIF** (salt-split): epidermal base (roof of blister like BP)
- **Fetal risk:**  $\uparrow$  risk of prematurity,  $\uparrow$  incidence of small for gestational age birth, up to 10% risk of skin involvement
- **Treatment:** oral corticosteroid (topical corticosteroid and antihistamine typically ineffective)
- **Association:**  $\uparrow$  incidence of anti-thyroid antibodies,  $\uparrow$  frequency with HLA-DR3, HLA-DR4

Most important pregnancy dermatosis to exclude



**Figure 3.39**

**A: Pemphigoid gestationis\***

**B: Pemphigoid gestationis\***

**C: Pemphigoid gestationis\***

\*Reprint from Ingber A. *Obstetric Dermatology: A Practical Guide*. New York, NY: Springer; 2008

**Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)**

(Figure 3.40A, B)

- Most common pregnancy-related dermatosis; late third trimester ( $\pm$  immediate postpartum) in first pregnancies (primigravida); risk  $\uparrow$  with twins and maternal obesity; diagnosis of exclusion
- Presents with intensely pruritic papules arising within striae of abdomen (sparing periumbilical area unlike PG),  $\pm$  vesicles, target or annular lesions; typically does not recur with subsequent pregnancies
- **Histology:** nonspecific findings including epidermal changes (spongiosis, parakeratosis) and perivascular lymphocytic infiltrate with dermal edema
- **DIF:** negative
- **Fetal risk:** none
- **Treatment:** anecdotal; potent topical corticosteroids and oral antihistamine, resolution 7–10 days after delivery

**Prurigo of Pregnancy** (Figure 3.40C)

- Benign dermatosis with unknown etiology; typically in second or third trimester
- Presents with excoriated papules and sometimes pustules (may be follicular) over extensor surfaces, but no bullae
- **Histology:** nonspecific
- **DIF/IIF:** negative
- **Fetal risk:** none
- **Treatment:** topical corticosteroid (anecdotal); resolves in postpartum period

**Cholestasis of Pregnancy**

- Benign dermatosis due to cholestasis; multifactorial and typically in third trimester ( $\pm$  second trimester)
- Presents with intense generalized pruritus (worse at night, worse on trunk/palms/soles),  $\pm$  dark urine, light-colored stools, jaundice; resolves 1–2 weeks after delivery,  $\pm$  recurrence with subsequent pregnancies and OCPs,  $\uparrow$  risk of cholelithiasis or gallbladder disease
- **Histology:** not needed (diagnosis per labs)
- **Labs:**  $\uparrow$  serum bile acids,  $\uparrow$  direct bilirubin
- **Fetal risk** (controversial):  $\uparrow$  incidence of stillbirth, meconium staining and premature labor
- **Treatment:** cholestyramine, ursodeoxycholic acid (UDCA), phototherapy, vitamin K supplementation if intrahepatic cholestasis  $>$  few weeks (causes impaired K absorption and prolonged PT); resolves 1–2 days after delivery

**Figure 3.40****A: PUPPP diagram\*****B: PUPPP\*****C: Prurigo of pregnancy\***

\*Reprint from Ingber A. *Obstetric Dermatology: A Practical Guide*. New York, NY: Springer; 2008

**Impetigo Herpetiformis (Pustular Psoriasis of Pregnancy)**

- Considered pustular psoriasis variant during pregnancy; late first trimester to third trimester
- Presents typically with pustules on erythematous base initially in inter-triginous areas,  $\pm$  fever, chills, malaise; recurrence with OCPs, menses, subsequent pregnancies
- **Histology:** same as pustular psoriasis
- **Fetal risk:** placental insufficiency
- **Labs:** hypocalcemia,  $\uparrow$  ESR,  $\uparrow$  leukocytosis
- **Treatment:** oral corticosteroid, treat hypocalcemia; resolves in postpartum period

**3.9 VASCULITIDES AND VASO-OCCLUSIVE DISEASES****Cutaneous Small Vessel Vasculitis (CSVV)** (Figure 3.41A, B)

- General term encompassing diseases with histopathologic features of leukocytoclastic vasculitis (perivascular neutrophilic infiltration and fibrinoid degeneration of vascular walls) involving only small cutaneous blood vessels irrespective of etiology; typically occurs 7–10 days after exposure to inciting agent
- CSVV often related to one of the following:
  - **Infection** (bacterial, viral) – 15–20%
  - **Inflammatory disorder** (autoimmune connective tissue disease, inflammatory bowel disease, seronegative spondyloarthropathy) – 15–20%
  - **Drug-exposure** – 10–15%
    - Common: NSAIDs, COX-2 inhibitors, leukotriene inhibitors, penicillins, quinolones, anti-TNF agents, G-CSF, hydralazine, anti-thyroid agents
    - Occasional: ACEI, allopurinol, furosemide, coumarin, quinine, macrolide antibiotics, thiazides, sulfonlureas, trimethoprim-sulfamethoxazole, vancomycin, IFN,  $\beta$ -blockers
  - **Neoplasms** – 5%
  - **Idiopathic** – 50%
- Presents with palpable purpuric to erythematous papules, vesicles, and macules over lower extremities and other dependent areas,  $\pm$  fever, arthralgias, myalgias and weight loss; extracutaneous involvement typically mild; prognosis depends on severity of systemic involvement
- Histology: leukocytoclastic vasculitis
- Treatment: rule out systemic vasculitis, remove any trigger, supportive therapy (90% spontaneous resolution)

**Figure 3.41****A: CSVV**

(Courtesy of Dr. Paul Getz)

**B: CSVV**

(Courtesy of Dr. Paul Getz)

**C: Urticarial vasculitis**

(Courtesy of Dr. Iris K. Aronson)



**Urticarial Vasculitis (UV)** (Figures 3.41C and 3.42A)

- Entity with clinical presentation resembling urticaria but with histopathological findings of LCV; may be associated with autoimmune connective tissue disease (i.e. SLE), infection (HBV, HCV, EBV), serum sickness, malignancy or medication (KI, NSAIDs, fluoxetine)
- Majority normocomplementemic with benign course (average duration 3 years); approximately 25% with hypocomplementemic UV and increased likelihood of systemic involvement
- Presents with urticarial papules and plaques lasting >24 h with associated burning or pain,  $\pm$  residual hemorrhage;  $\pm$  fever, malaise, intermittent arthralgias, pulmonary, and GI symptoms (hypocomplementemic)
- Labs (hypocomplementemic form):  $\downarrow$  complement levels, anti-C1q antibody
- Histology: leukocytoclastic vasculitis, but typically subtle
- Treatment: antihistamines, NSAIDs, colchicine, dapsone, antimalarial, oral corticosteroid

Schnitzler's syndrome: urticarial vasculitis + monoclonal IgM gammopathy + at least 2 of the following: fever, arthralgias, HSM,  $\uparrow$  ESR,  $\uparrow$  WBC, bone abnormality, bone pain)

**Henoch-Schönlein Purpura (HSP)**

- Specific type of cutaneous small vessel vasculitis
- Presents with palpable purpura with predilection for lower extremities and buttocks; arthritis, hematuria, colicky abdominal pain,  $\pm$  GI bleeding and vomiting
- Histology: leukocytoclastic vasculitis; DIF with perivascular IgA, C3 and fibrin
- Typically occurs after respiratory tract infection in children (much lower incidence in adults); 2% may develop permanent renal impairment
- Treatment: mainly supportive as typically self-limited

**Erythema Elevatum Diutinum (EED)** (Figure 3.42B)

- Presents with red, violaceous or brown papules and plaques favoring extensor surfaces; associated arthralgias
- Histology: LCV with neutrophilic infiltrate in early lesions; fibrosis and lipid deposits with cholesterol clefts in older lesions
- Associated with autoimmune diseases, infections (hemolytic strep, HBV, HIV), inflammatory bowel disease, hematologic disorders (IgA monoclonal gammopathy); lesions thought to be related to immune complex deposition in blood vessels with damage to vessels
- Treatment: dapsone treatment of choice

**Granuloma Faciale** (Figure 3.42C)

- Presents with smooth violaceous to red-brown plaque on face, typically solitary but may see multiple on face (rarely extra-facial sites involved)
- Histology: normal epidermis, grenz zone above diffuse infiltrate of neutrophils, eosinophils, histiocytes and lymphocytes; leukocytoclastic vasculitis, often hemosiderin within dermis
- Treatment: often resistant; IL corticosteroid, dapsone, clofazamine, topical tacrolimus

**Figure 3.42****A: Urticarial vasculitis**

(Courtesy of Dr. Iris K. Aronson)

**B: EED\*****C: Granuloma faciale\***

\* Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009



### Cryoglobulinemia

- Presence of serum cryoglobulins (single or mixed immunoglobulins that can undergo reversible precipitation at low temperatures)
- Types II/III have rheumatoid factor (RF) activity and bind to polyclonal immunoglobulins; immune complexes form from circulating cryoglobulins and are subsequently deposited within blood vessel walls causing vasculitis
- Histology: leukocytoclastic vasculitis
- Treatment: directed at any underlying disease (i.e. HCV: IFN $\alpha$  + ribavirin)

Cryofibrinogenemia: cryoprecipitate in plasma made up primarily of fibrinogen; can be primary or secondary to malignancy, autoimmune connective tissue disease or infection; presents with leg ulcers, livedo reticularis or purpura

Type	Immunoglobulins	Underlying Associations	Clinical Findings
I	Monoclonal IgM or IgG (no rheumatoid factor activity)	<b>Lymphoproliferative disorders (LPD)</b> , plasma cell dyscrasias	Raynaud's phenomenon, purpura, acrocyanosis, arterial thrombosis
II (Mixed)	Monoclonal IgM (or IgG) with polyclonal IgG	<b>HCV</b> , autoimmune connective tissue diseases, LPD	Vasculitis with palpable purpura, arthralgias, glomerulonephritis, peripheral neuropathy
III (Mixed)	Polyclonal IgM complexed with polyclonal IgG		IFN treatment worsens peripheral neuropathy

### Churg-Strauss

- Granulomatous small vessel vasculitis affecting mainly blood vessels of lungs (severe asthma, allergic rhinitis), GI tract, and peripheral nerves,  $\pm$  skin and heart
- Skin findings include palpable purpura, subcutaneous nodules, livedo reticularis, and urticaria
- Labs:  $\uparrow$  IgE, p-ANCA (anti-myeloperoxidase {MPO})
- Treatment: oral corticosteroids  $\pm$  cytotoxic agents

**ANCA** (anti-neutrophil cytoplasmic antibodies): autoantibodies against various lysosomal enzymes

### Wegener's Granulomatosis (Figure 3.43)

- Granulomatous systemic vasculitis with inflammation of respiratory tract (upper/lower) and glomerulonephritis
- May present with mucocutaneous findings including palpable purpura, oral ulcers, red friable gingiva, painful ulcers or nodules mimicking pyoderma gangrenosum
- Labs:  $\uparrow$  ESR, WBC, c-ANCA (anti-proteinase-3 {PR-3})



**Figure 3.43**

#### Wegener's granulomatosis

(Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

### Polyarteritis Nodosa (PAN)

- Multisystem segmental necrotizing vasculitis of medium-sized vessels; cutaneous PAN (variant) limited to skin
- Cutaneous findings include 'punched out' ulcers, livedo reticularis, subcutaneous nodules, and acral gangrene
- Association: inflammatory disease (IBD, SLE) or infection (HBV, strep)

**Table 3-23 Vaso-Occlusive Diseases**

Entity	Clinical Findings	Histology/Treatment
<b>Livedoid vasculopathy</b> (Atrophie blanche)	Painful ulcerations on lower legs ± with surrounding livedo reticularis → heal with <b>atrophic hypopigmented scars</b> (atrophie blanche)	Histology: superficial <b>dermal vessels with hyalinized walls</b> , thrombi, mild perivascular infiltrate Treatment: antiplatelet, anticoagulant and fibrinolytic therapies
<b>Cholesterol emboli</b> (Figure 3.45E)	Findings include livedo reticularis, peripheral gangrene, ulceration, nodules, cyanosis, retiform purpura	Histology: <b>elongated cholesterol clefts within small vessels</b> , thrombi Treatment: supportive treatment, ± antiplatelet agents
<b>Anti-phospholipid syndrome (APS)</b> (Figure 3.45D)	Findings include livedo reticularis, Raynaud's phenomenon, vasculitis-like lesions, splinter hemorrhages  Labs: <b>anti-β2 glycoprotein, lupus anticoagulant, anti-cardiolipin antibodies</b>	Histology: noninflammatory small vessel thrombosis Treatment: anticoagulation, antiplatelet agents
<b>Sneddon's syndrome</b>	Persistent livedo reticularis associated with systemic arterial thrombi; labile hypertension, recurrent neurologic symptoms  Can be manifestation of APS or distinct entity (skin/brain only)	Histology: partial or complete occlusion of small vessels Treatment: warfarin
<b>Malignant atrophic papulosis</b> (Degos disease) (Figure 3.45F)	Crops of small erythematous papules → porcelain white scars (similar to atrophie blanche); GI and CNS symptoms	Histology: <b>wedge-shaped dermal infarct, thrombosed arteriole</b> (typically in subcutaneous fat) Treatment: no proven treatment; aspirin ± pentoxifylline

### 3.10 EOSINOPHILIC AND NEUTROPHILIC DERMATOSES

**Table 3-24 Eosinophilic and Neutrophilic Dermatoses**

Entity	Clinical Findings	Histology/Treatment
<b>Eosinophilic Dermatoses</b>		
<b>Eosinophilic pustular folliculitis</b> (Ofuji's disease) (Figure 3.44C)	Erythematous follicular papules, pustules, and plaques with annular or serpiginous pattern, occurring in recurrent crops; typically on face in men, associated pruritus	Histology: ↑↑ eosinophils around follicles, exocytosis of eosinophils and lymphocytes into follicular epithelium Treatment: indomethacin (first line), dapsone, phototherapy, oral corticosteroid or minocycline (topical steroid if mild)
<b>Eosinophilic folliculitis</b> (AIDS-associated) (Figure 3.44B)	Follicular papules erupting over face, ± scalp and upper trunk; associated with significant pruritus and ↓↓ <b>CD4 count</b>	Histology: similar to Ofuji's disease Treatment: antiretroviral therapy to ↑ CD4 count, phototherapy, topical corticosteroid with oral antihistamine
<b>Angiolymphoid hyperplasia with eosinophilia</b> (Figure 3.44A)	Red to pink to brown papules or nodules typically over scalp, around ears or forehead, ± grouped, ± painful	Histology: vascular proliferation with ' <b>hobnail</b> ' endothelial cells (protrude into lumen), surrounding eosinophils Treatment: surgical excision (1/3 recur)
<b>Neutrophilic Dermatoses</b>		
<b>Behçet's disease</b> (Figure 3.44D–F)	Ulcerations; acneiform, papulopustular, EN-like or pseudofolliculitis-type lesions; ± arthritis, neurologic involvement, bowel aphthae, thrombophlebitis; <b>HLA-B51</b>	Histology: ulcerated epidermis or superficial pustule, diffuse neutrophilic infiltrate in dermis, ± lymphocytes, histiocytes, sometimes vasculitis Treatment: colchicine, dapsone, thalidomide, TNF-inhibitors
<b>Diagnostic criteria:</b> oral ulcers (at least three times in 12 month period) PLUS at least two of the following: - recurrent genital ulcers - positive pathergy test - ocular (uveitis, retinal vasculitis) - skin findings (see above)		
<b>Sweet's syndrome</b> (Figure 3.45A)	Tender, erythematous edematous papules and plaques typically over face or upper extremities; ± fever, malaise, leukocytosis; <u>vesicobullous variant</u> frequently associated with <u>myelogenous leukemia</u>	Histology: variable epidermal changes, superficial dermal edema with diffuse neutrophilic infiltrate ± lymphocytes, histiocytes, eosinophils, no true vasculitis Treatment: oral corticosteroid × 4–6 weeks, KI, dapsone, colchicine; 30% recurrence
<b>Diagnostic criteria:</b> abrupt-onset of typical eruption + typical histopathological findings PLUS 2 of following: 1. preceded by associated infection/vaccination, drug exposure, current malignancy/inflammatory disorder or pregnancy 2. fever and constitutional symptoms 3. leukocytosis 4. excellent response to systemic corticosteroids		
<b>Pyoderma gangrenosum</b> (Figure 3.45B, C)	Tender papulopustule with violaceous induration → bulla or expanding ulcer w/ purulent base, undermined border; cribriform scar; pustular, bullous, granulomatous variants	Histology: early lesions with leukocytoclasia, neutrophilic infiltrate, advanced lesions with marked necrosis of tissue with infiltrate of mononuclear cells Treatment: none with consistent efficacy; oral corticosteroid ± steroid-sparing agents
<u>Vesicobullous type</u> most common with acute or chronic myelogenous leukemia	50% PG with systemic disease: IBD, arthritis or <b>hematological disorders</b> (if monoclonal gammopathy, usually <b>IgA</b> )	



**Figure 3.44**

**A: Angiolymphoid hyperplasia with eosinophilia**

(Reprint from Baykal C, Yazganoglu K. *Dermatological Diseases of the Nose and Ears*. Berlin: Springer; 2010)

**B: Eosinophilic folliculitis (AIDS-related)**

(Reprint from Mildvan D (Ed). *International Atlas of AIDS*. New York, NY: Springer; 2008)

**C: Eosinophilic pustular folliculitis**

(Courtesy of Dr. Sophie M. Worobec)

**D: Behcet's disease**

(Courtesy of Dr. Paul Getz)

**E: Behcet's disease**

(Courtesy of Dr. Paul Getz)

**F: Behcet's disease**

(Courtesy of Dr. Paul Getz)





**Figure 3.45**

**A: Sweet's syndrome**

(Courtesy of Dr. Iris K. Aronson)

**B: Pyoderma gangrenosum**

(Courtesy of Dr. Paul Getz)

**C: Pyoderma gangrenosum**

(Courtesy of Dr. Sophie M. Worobec)

**D: Livedo reticularis**

**E: Cholesterol embolus**

(Courtesy of Dr. Paul Getz)

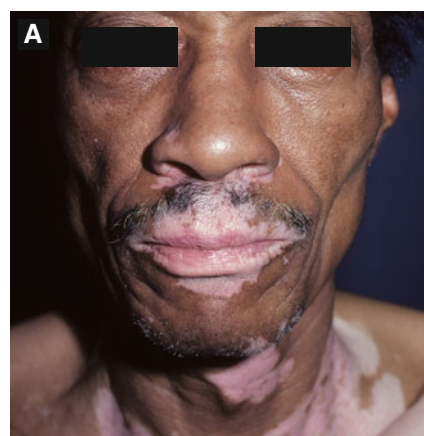
**F: Degos disease**

(Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)

### 3.11 PIGMENTARY DISORDERS AND VITAMIN DEFICIENCIES

#### **Vitiligo** (Figure 3.46A)

- Acquired pigmentary disorder of skin and mucous membranes with multifactorial etiology (genetic and non-genetic), likely due to autoimmune destruction of melanocytes in affected skin
- Presents with depigmented macules or patches surrounded by normal skin; ↑ accentuation with Wood's lamp; predilection for periorificial facial areas, bony prominences and sites with ↑ trauma; may be classified into
  - Localized: focal, unilateral, and mucosal
  - Generalized: wide distribution, acrofacial, and mixed
  - Universal: near complete to complete depigmentation
- Treatment: NB-UVB, PUVA, topical corticosteroid, topical calcineurin inhibitor, pseudocatalase, excimer laser, surgical therapy
- May be associated with autoimmune endocrinopathy such as thyroid dysfunction (Graves' disease, Hashimoto's thyroiditis) and polyglandular dysfunction; anecdotal reports with pernicious anemia and Addison's disease



#### **Melasma (Chloasma)** (Figure 3.46B)

- Acquired hyperpigmentation in sun-exposed areas primarily seen in women (90%) and darker skin types
- ↑ Incidence with pregnancy, OCP use, sun-exposure
- Presents with tan to dark brown to brown gray irregular patches primarily on face (malar, mandibular and centrofacial patterns); worsens during summer time
- Treatment: sun protection, hydroquinone, tretinoin, combination of tretinoin/topical corticosteroid/hydroquinone (Triluma®), chemical peel



#### **Erythema Dyschromicum Perstans (Ashy Dermatitis)**

- Benign skin condition with unknown etiology presenting with circular, irregular or oval gray to blue-brown macules/patches on trunk, ± upper extremities and face
- Histology: vacuolar degeneration, pigment incontinence
- Treatment: no consistently effective treatment

#### **Erythema Ab Igne** (Figure 3.46C)

- Reticulated hyperpigmentation due to chronic exposure to infrared radiation (laptop computer, heating pad, etc.)
- Presents with reticulated erythema which over time becomes hyperpigmented, ± bullae, ± hyperkeratosis
- Treatment: remove heat source, anecdotal treatment with 5-FU



**Figure 3.46**

**A: Vitiligo**

(Courtesy of Dr. Paul Getz)

**B: Melasma**

(Courtesy of Dr. Paul Getz)

**C: Erythema ab igne**

(Courtesy of Dr. Sophie M. Worobec)

**Table 3-25 Nutritional Deficiencies**

Deficiency	Clinical Findings	Other
<b>Water Soluble</b>		
<b>Vitamin C</b> (Figure 3.47D) Scurvy	Follicular hyperkeratosis, <b>corkscrew hairs</b> , <b>perifollicular hemorrhage</b> , petechiae, epistaxis, gingivitis, delayed wound healing, hemorrhage (intramuscular/intraarticular)	Fxn: role in collagen/ground substance formation and enzymatic processes Misc: deficiency in alcoholics, fad diets, malnutrition
<b>Vitamin B<sub>1</sub></b> (Thiamine) Beriberi	Glossitis, peripheral neuropathy ('dry' beriberi), congestive heart failure ('wet' beriberi), Korsakoff's syndrome, Wernicke's encephalopathy	Fxn: coenzyme in carbohydrate metabolism and role in formation of glucose Misc: deficiency with polished rice diet, alcoholics, GI diseases, hyperthyroidism, prolonged diarrhea, malnutrition
<b>Vitamin B<sub>2</sub></b> (Riboflavin) Oral-ocular-genital syndrome	<b>Angular cheilitis</b> ; atrophic, sore, <b>magenta-colored tongue</b> ; seborrheic dermatitis-like changes (nose, mouth, eyes), genital dermatitis, photophobia, conjunctivitis	Fxn: energy production, enzyme function, normal fatty acid and amino acid synthesis, reproduction of glutathione Misc: deficiency with celiac sprue, alcoholics, poor nutrition
<b>Vitamin B<sub>3</sub></b> (Niacin or nicotinic acid) (Figure 3.47A) Pellagra	3Ds: dermatitis, diarrhea, dementia <b>Photosensitive eruption</b> on face, neck, and upper chest ( <b>Casal's necklace</b> ), angular cheilitis, stomatitis, perianal dermatitis, diarrhea, disorientation and coma	Fxn: involved in reduction-oxidation reactions; tryptophan precursor amino acid Misc: deficiency associated with diet of entirely corn, alcoholics, use of isoniazid (INH), chronic colitis or diarrhea, carcinoid syndrome
<b>Vitamin B<sub>6</sub></b> (Pyridoxine)	Seborrheic dermatitis-like periorificial eruption, atrophic glossitis, angular cheilitis, conjunctivitis, dementia, <b>peripheral neuropathy</b>	Fxn: role in amino acid and fatty acid metabolism Misc: deficiency associated with cirrhosis, uremia, medications ( <b>INH</b> ), malnutrition
<b>Vitamin B<sub>12</sub></b> (Cobalamin) (Figure 3.47B)	Generalized hyperpigmentation, megaloblastic anemia, glossitis (bright red atrophic tongue), paresthesias, peripheral neuropathy, irritability; ↑↑ body stores so may take years to develop symptoms	Fxn: role in DNA synthesis and neurologic function Misc: deficiency associated with GI abnormalities (pernicious anemia) and malabsorption, strict vegetarianism
<b>Folic acid</b>	<b>Diffuse hyperpigmentation (patchy)</b> , cheilitis, glossitis and megaloblastic anemia similar to changes with B12 deficiency	Fxn: involved in DNA synthesis Misc: deficiency associated with elderly patients, drugs (methotrexate), malnutrition
<b>Biotin</b>	Similar to zinc deficiency symptoms: periorificial eruption, conjunctivitis, depression, paresthesias, alopecia, seizures	Fxn: essential cofactor for several carboxylases Misc: acquired or inherited; deficiency seen w/ ingestion of raw egg whites (avidin binds biotin), short gut or malabsorption

*Continued on the next page*



Table 3-25 Nutritional Deficiencies (cont'd)

Deficiency	Clinical Findings	Other
<b>Fat Soluble</b>		
Vitamin A Phrynoderma	<b>Keratotic follicular papules</b> (resembling keratosis pilaris), xerosis, <b>night blindness</b> , <b>Bitot's spots</b> (foamy white spots on conjunctiva), keratomalacia, and changes in bone tissue	Fxn: req'd for normal keratinization of epithelial tissue, controls protein expression Work-up: check <b>serum retinol</b> (vit. A) level Misc: excess vitamin A levels have symptoms similar to synthetic retinoid therapy (alopecia, cheilitis, xerosis)
Vitamin D	Alopecia (no other skin manifestations); rickets (children) and osteomalacia (adults)	Fxn: regulates calcium and phosphate metabolism Misc: synthesized in skin UVB + 7-dehydrocholesterol → Vit D3
Vitamin K	Impairment of coagulation cascade with <b>prolonged PT</b> ; purpura, ecchymoses, hemorrhage	Fxn: necessary to synthesize coagulation factors ( <b>II, VII, IX, X</b> ) and protein <b>C</b> and <b>S</b> Misc: deficiency with liver disease, malabsorption, cystic fibrosis, biliary disease, drugs (warfarin, cephalosporins, salicylates)
dehydrocholesterol (epidermal) absorbs UVB → vitamin D3 (cholecalciferol) → hydroxylated by liver, forms 25-(OH)D3 → hydroxylated by kidney, forms 1, 25-(OH)2D3 (calcitriol, active form)		
<b>Other</b>		
Essential fatty acids (EFA)	Dry scaly almost leathery skin, poor wound healing, capillary fragility, increased infections, diffuse alopecia, failure to thrive  EFA: unsaturated fatty acids; includes linoleic, linolenic, and arachidonic acid (latter also metabolized from linoleic acid)	Fxn: serve as precursor to prostaglandins, enzyme storage and proper lamellar granule formation Misc: body cannot synthesize unsaturated FAs so must be obtained from diet; deficiency with TPN, malnutrition, aggressively low fat diets
Iron	Pallor, koilonychia (spoon-shaped nails), glossitis, angular cheilitis, pruritus, fatigue, alopecia (telogen effluvium)	Fxn: transport of oxygen (hemoglobin), integral to several enzyme reactions Misc: iron absorption from proximal small intestine; deficiency with decreased intake, excessive loss as with bleeding
Zinc (Figure 3.47C)	Seborrheic dermatitis-like eruption in periorificial and perianal areas; periorificial and acral bullae; angular cheilitis, diarrhea, alopecia, poor wound healing, mental disturbances	Fxn: critical role in metalloenzymes involved in synthesis/degradation of lipids, nucleic acid and protein Misc: inherited (see pediatric chapter) or acquired (alcoholics, malabsorption, inflammatory bowel disease, chronic renal failure)
Marasmus	Dry, wrinkled and hyperpigmented skin, ↓ subcutaneous fat, thin hair, ↑ lanugo hair, 'monkey facies' or aged appearance, purpura	Due to prolonged deficiency of both protein and calories
Kwashiorker	<b>Edema</b> (characteristic <b>potbelly</b> ), dry hair with red-tinge, ± 'flag sign', superficial desquamation, pallor, dyschromia, petechiae	Protein deficiency, normal caloric intake 'Flag sign': bands of light color alternating with normal darker hair color



### 3.12 CUTANEOUS MANIFESTATIONS OF SYSTEMIC DISEASES

**Table 3-26 Paraneoplastic Cutaneous Manifestations**

Entity	Clinical Findings	Underlying Cancer
<b>Acanthosis nigricans (AN)</b> (Figure 3.48A)	Velvety hyperpigmentation (body folds)	Most common: GI adenocarcinoma (gastric)
<b>Acquired angioedema</b> (Figure 3.50C)	Angioedema without urticaria	Lymphoproliferative diseases
<b>Acquired ichthyosis</b>	Diamond-shape scale (often legs)	Lymphoma (Hodgkin and NHL)
<b>Alopecia neoplastica</b>	Cicatricial localized loss of hair	Breast cancer (metastatic)
<b>Primary amyloidosis</b> (Figure 3.49A)	Periorbital 'pinch' purpura	Multiple myeloma (one fourth of cases)
<b>Bazex sign</b> (Acrokeratosis neoplastica) (Figure 3.50A)	Psoriasiform plaques on palms, soles, nose and ear helices	Upper aerodigestive tract carcinoma
<b>Carcinoid syndrome</b>	Head/neck flushing, pellagra-like dermatitis, erythema	Mid-gut tumors (w/ liver metastases), gastric/bronchial carcinoid tumors
	↑ 5-HIAA levels (hydroxyindoleacetic acid), a serotonin metabolite	
<b>Cryoglobulinemia</b>	Purpura, acrocyanosis, livedo reticularis	Lymphoplasmocytic disorders
<b>Dermatomyositis</b>	Gottron's papules, poikiloderma	GI and ovarian cancer
<b>Erythema gyratum repens</b> (Figure 3.50D)	Gyrate polycyclic plaques with trailing scale	Various malignancies, bronchogenic carcinoma most common
<b>Hypertrichosis lanuginosa acquisita</b>	Sudden growth of soft, downy hair in adult	Lung and colon cancer
<b>Metastases, cutaneous</b> (Figure 3.49F)	Pink/violaceous papules/nodules	Most common: <b>breast and lung</b>
<b>Multicentric reticulohistiocytosis</b> (Figure 3.49D)	Erythematous papules mainly over face and dorsal hands; arthritis	Various malignancies (30% with underlying cancer)
<b>Necrolytic migratory erythema (NME)</b>	Erythematous patches with bullae over face, groin and abdomen (severe intertrigo)	Pancreatic carcinoma ( $\alpha$ -cell tumor)
		<u>Glucagonoma syndrome</u> : glucagon-secreting carcinoma, NME, weight loss, glossitis, DM
<b>Necrobiotic xanthogranuloma</b>	Yellow plaque commonly seen periorbitally	Paraproteinemia, occasionally myeloma
<b>Nodular fat necrosis</b>	Subcutaneous nodules (legs)	Pancreatic carcinoma
<b>Paget's disease</b> (Figure 3.49B)	Eczematous to psoriasiform plaque	Adnexal, breast, GU or GI cancer
<b>Paraneoplastic pemphigus</b>	Erosive disease of mucous membranes	Lymphoma, CLL
<b>Pruritus</b>	Localized or generalized	Hodgkin's lymphoma mainly
<b>Pyoderma gangrenosum</b> (Figure 3.49E)	Rapidly expanding ulceration with undermined border	Hematologic malignancy (especially atypical bullous form)
<b>Sign of Leser-Trélat</b>	Sudden onset of multiple seborrheic keratoses	Various malignancies: carcinoma (gastric, colon, breast) and lymphoma
<b>Sweet's syndrome</b>	Erythematous, pseudovesicular papules, nodules and plaques	Acute myelogenous leukemia, less commonly lymphoma
<b>Tripe palms</b> (Acanthosis palmaris) (Figure 3.49C)	Thickened, velvety palms with pronounced dermatoglyphics	Lung cancer (if only palms), gastric cancer (if palms + AN)
<b>Xanthoma, plane</b>	Yellow, thin plaques favoring trunk, periorbital and body folds	Monoclonal gammopathy including multiple myeloma

**Table 3-27 Cutaneous Signs in Select Internal Diseases**

Endocrine	
<b>Diabetes mellitus</b>	<ul style="list-style-type: none"> <li>– Acanthosis nigricans</li> <li>– Bullous diabeticorum: (Figure 3.48B) tense noninflammatory blisters on lower extremities</li> <li>– Diabetic dermopathy: atrophic yellow to brown macules on lower legs</li> <li>– Disseminated granuloma annulare</li> <li>– Necrobiosis lipoidica diabeticorum</li> <li>– Scleredema of Buschke</li> <li>– Eruptive xanthomas (Figure 3.48F)</li> </ul>
<b>Hypothyroidism</b>	<ul style="list-style-type: none"> <li>– Coarse dry skin</li> <li>– Generalized myxedema: boggy and edematous</li> <li>– Dull, brittle hair</li> <li>– Alopecia of lateral 1/3 eyebrows (madarosis)</li> <li>– Onycholysis</li> </ul>
<b>Hyperthyroidism (Graves' disease)</b>	<ul style="list-style-type: none"> <li>– Velvety, smooth or moist skin</li> <li>– Hyperpigmentation (localized or generalized)</li> <li>– Pretibial myxedema: (Figure 3.48E) yellow-brown waxy papules on lower extremities</li> <li>– Fine hair</li> <li>– Mild but diffuse alopecia</li> <li>– Koilonychia</li> <li>– Onycholysis</li> </ul>
<b>Addison's disease</b>	<ul style="list-style-type: none"> <li>– Hyperpigmentation</li> </ul>
GI	
<b>Cirrhosis</b>	<ul style="list-style-type: none"> <li>– Spider angiomas</li> <li>– Palmar erythema</li> <li>– Gynecomastia</li> <li>– Terry's nails</li> </ul>
<b>Hemochromatosis</b>	<ul style="list-style-type: none"> <li>– Generalized hyperpigmentation</li> </ul>
<b>Primary biliary cirrhosis</b>	<ul style="list-style-type: none"> <li>– Pruritus</li> <li>– Eruptive/planar xanthomas</li> </ul>
<b>Wilson's disease</b>	<ul style="list-style-type: none"> <li>– Kayser-Fleischer rings</li> <li>– Blue lunulae</li> </ul>
<b>Hepatitis C</b>	<ul style="list-style-type: none"> <li>– Mixed cryoglobulinemia</li> <li>– Porphyria cutanea tarda</li> <li>– Lichen planus (particular oral) (Figure 3.48C)</li> <li>– Pruritus</li> <li>– Necrolytic acral erythema</li> <li>– Polyarteritis nodosa</li> </ul>
<b>Inflammatory bowel disease</b>	<ul style="list-style-type: none"> <li>– Erythema nodosum (Figure 3.48D)</li> <li>– Pyoderma gangrenosum (also oral pyostomatitis vegetans)</li> </ul>
Renal	
<b>End stage renal disease</b>	<ul style="list-style-type: none"> <li>– Pruritus</li> <li>– Uremic frost</li> <li>– Calciphylaxis</li> <li>– Acquired perforating disorder (Figure 3.50B)</li> <li>– Nephrogenic systemic fibrosis</li> </ul>



**Figure 3.47**

**A: Pellagra** (Courtesy of Dr. Paul Getz)

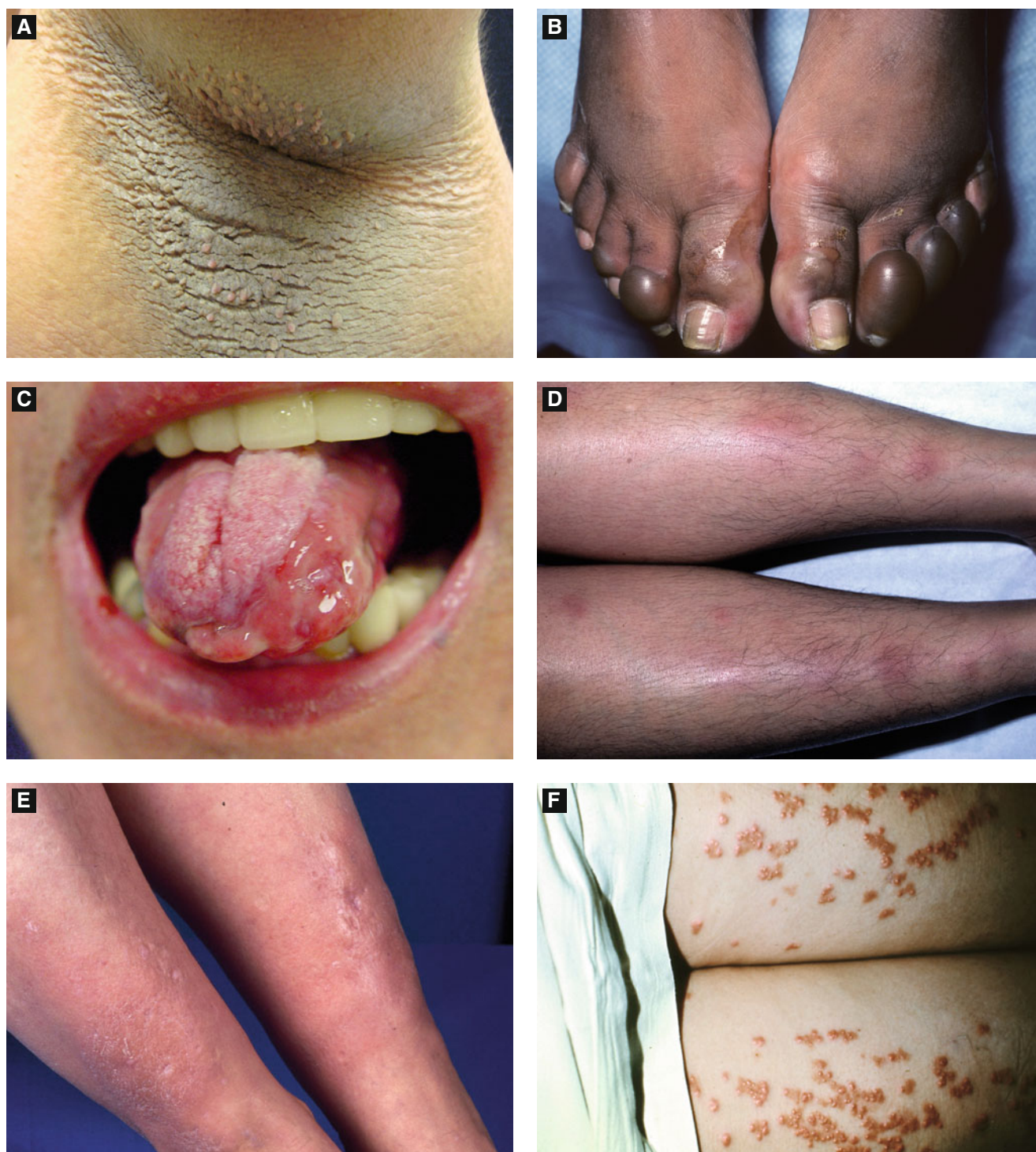
**B: Glossitis** (Courtesy of Dr. Paul Getz)

**C: Zinc deficiency with acral bulla** (Courtesy of Dr. Paul Getz)

**D: Scurvy ('corkscrew' hairs, perifollicular hemorrhage)**

(Reprint from Feldman M, ed. *Gastroenterology and Hepatology*. Philadelphia, PA: Churchill Livingstone, Inc; 1998)





**Figure 3.48**

**A: Acanthosis nigricans**

**B: Bullous diabeticorum**

(Courtesy of Dr. Paul Getz)

**C: Oral lichen planus**

(Courtesy of Dr. Iris K. Aronson)

**D: Erythema nodosum**

(Courtesy of Dr. Paul Getz)

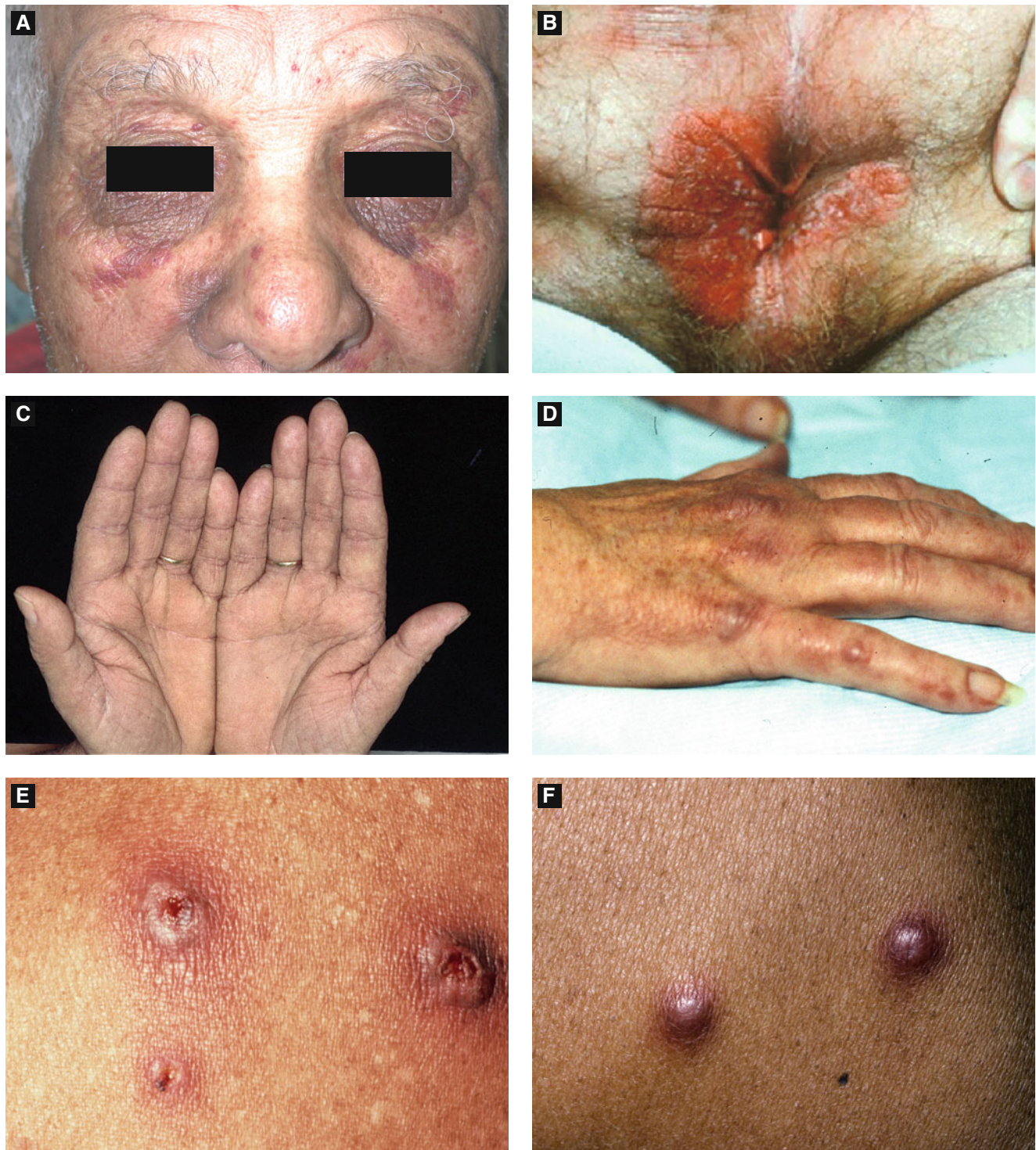
**E: Pretibial myxedema**

(Reprint from Krause W. *Cutaneous Manifestations of Endocrine Diseases*. London: Springer; 2009)

**F: Eruptive xanthomas**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)





**Figure 3.49**

**A: Primary amyloidosis ('pinch' purpura)**

**B: Paget's disease**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**C: Tripe palms**

(Reprint from Krause W. *Cutaneous Manifestations of Endocrine Diseases*. London: Springer; 2009)

**D: Multicentric reticulohistiocytosis**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**E: Pyoderma gangrenosum**

(Courtesy of Dr. Paul Getz)

**F: Cutaneous metastases (bronchogenic carcinoma)**

(Courtesy of Dr. Paul Getz)





**Figure 3.50**

**A:** Bazex sign (acrokeratosis paraneoplastica)\*

**B:** Acquired perforating disorder (in ESRD)

**C:** Acquired angioedema (resolving)

\* Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. *Braun-Falco's Dermatology*. 3rd ed., Berlin: Springer; 2009

**D:** Erythema gyratum repens

(Courtesy of Dr. Paul Getz)

### 3.13 DISORDERS OF HAIR

#### A. NON-SCARRING ALOPECIAS

##### Alopecia Areata (Figure 3.51A)

- Most common non-scarring alopecia; unknown etiology but likely T cell-mediated autoimmune condition in patients with genetic predisposition
- Presents with round to oval alopecic non-scarring patches on scalp, ‘exclamation mark’ hairs; different patterns include patchy (most common), reticular, diffuse with generalized thinning, alopecia totalis (loss of entire scalp hair), alopecia universalis (loss of scalp and body hair), ophiasis pattern (band-like hair loss at periphery of temporal/occipital scalp)
- May have nail involvement (pitting most common)
- Histology: lymphocytes surrounding lower portion of hair follicle resembling ‘swarm of bees’, ↑ miniature telogen and catagen follicles
- Treatment: topical/intralesional corticosteroid, other topicals (squaric acid, anthralin, minoxidil), excimer laser, systemic corticosteroid or cyclosporine
- Associations: thyroid disease, vitiligo, atopy, IBD, IDDM, polyendocrinopathy

##### Trichotillomania (Figure 3.51B)

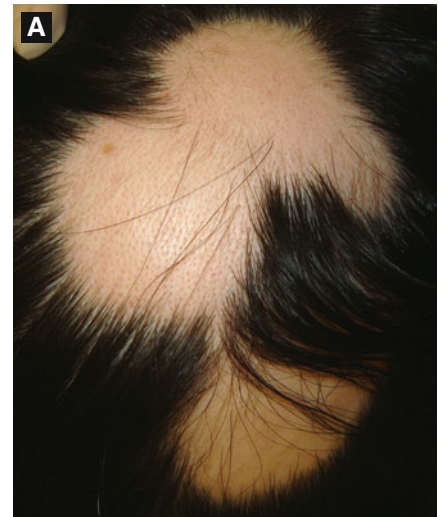
- Non-scarring alopecia due to habitual hair pulling typically in young girls, may be classified as obsessive-compulsive disorder
- Presents with alopecia of varying lengths of broken hair in localized area over scalp, eyebrows, or eyelashes
- Histology: deformed hair shafts (trichomalacia), empty follicles, pigmented hair casts in follicles, ± perifollicular infiltrate or fibrosis
- Treatment: behavior modification, SSRIs helpful

##### Telogen Effluvium (Figure 3.51C)

- Non-scarring alopecia with diffuse shedding of hair typically involving entire scalp, often due to trigger
- Triggers include pregnancy (typically 2–3 months after delivery), fever, chronic illness or severe stressor, diet or starvation, hypothyroidism, certain medications

##### Anagen Effluvium

- Sudden-onset loss of anagen hairs; triggers include chemotherapy, radiation, chemicals (thallium, arsenic)



**Figure 3.51**

**A: Alopecia areata**

**B: Trichotillomania**

(Courtesy of Dr. Paul Getz)

**C: Telogen effluvium**



**Triangular Alopecia** (Figure 3.52A)

- Either congenital or acquired during first decade (rarely may occur during adulthood)
- Presents with non-scarring triangular shaped alopecic patch involving temporal scalp, may be unilateral or bilateral

**Androgenetic Alopecia**

- Males with decreased hair density over bitemporal and vertex of scalp; females with mid frontoparietal scalp involvement (widened hair part, 'Christmas tree' pattern) but preservation of anterior hair line
- Androgen-dependent alopecia; testosterone converted to dihydrotestosterone (DHT) by  $5\alpha$ -reductase;  $\uparrow$  activity of DHT and  $5\alpha$ -reductase in men with androgenetic alopecia
- Histology: normal # of follicles,  $\uparrow$  vellus hairs, no significant inflammation,  $\uparrow$  telogen hairs (advanced stages)
- Treatment: minoxidil, finasteride, OCP, spironolactone, hair transplantation

**B. SCARRING ALOPECIAS****Central Centrifugal Cicatricial Alopecia (Hot Comb Alopecia)**  
(Figure 3.52B)

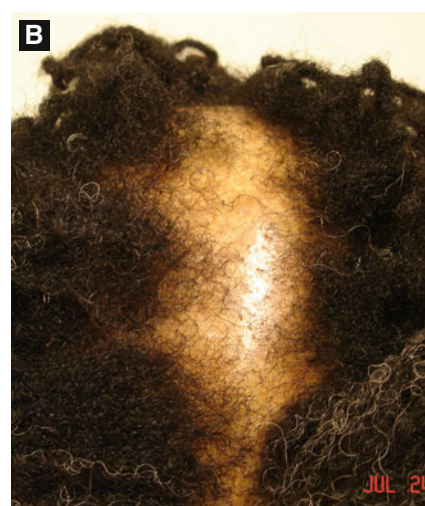
- Also known as follicular degeneration syndrome, pseudopelade of the central scalp, and folliculitis decalvans of the central scalp and vertex
- Scarring alopecia typically in African American women thought to be due to chemicals or heat leading to premature desquamation of inner root sheath
- Presents as alopecic ill-defined areas with scarring over crown or vertex with gradual expansion; inflammation might not be appreciated
- Histology: concentric lamellar fibroplasia of involved follicles, perifollicular inflammation, fragments of hair shaft and granulomatous inflammation (advanced cases)
- Treatment: high potency topical corticosteroid  $\pm$  oral antibiotic (tetracycline family, i.e. doxycycline)

**Lichen Planopilaris** (Figure 3.52C)

- Presents commonly with alopecic patches with perifollicular erythema;  $\pm$  tenderness or pruritus
- Histology: lichenoid lymphocytes around affected follicles with vacuolar degeneration within affected infundibula, perifollicular fibrosis
- Treatment: antimalarial, topical/intralesional corticosteroid

**Dissecting Cellulitis of Scalp (Perifolliculitis Capitis Abscedens Et Suffodiens)**

- Part of the follicular occlusion tetrad; typically occurring in young adult black men
- Presents with multiple, firm boggy nodules and plaques with purulent material
- Histology: dense perifollicular inflammation affecting lower half of dermis with resulting dense fibrosis
- Treatment: intralesional corticosteroid, oral antibiotic, surgery or oral isotretinoin (not always effective)

**Figure 3.52****A: Acquired triangular alopecia**  
(Courtesy of Dr. Iris K. Aronson)**B: Central centrifugal alopecia\*****C: Lichen planopilaris\***

\*Courtesy of Dr. Sophie M. Worobec

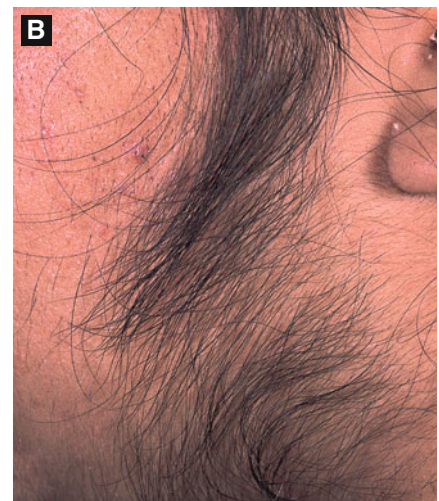


**Traction Alopecia** (Figure 3.53A)

- Alopecia due to sustained tension on scalp hair (i.e. tight braids, tight bun, etc.) with initially temporary non-scarring hair loss; however, with time may become permanent with scarring; lag period between tension and alopecia may be a decade or more
- Alopecia involving frontal and/or temporal scalp
- Histology: early cases consistent with trichotillomania; advanced cases with ↓ number of terminal hairs, connective tissue replacing follicles, no significant inflammation

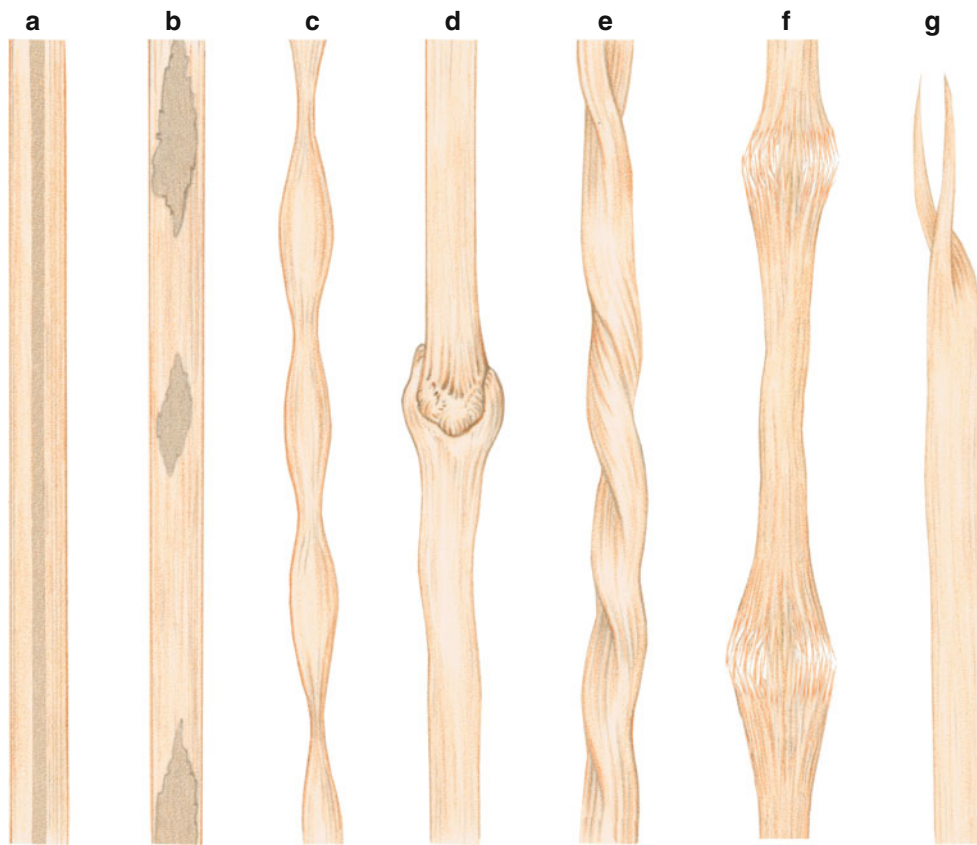
**C. HIRSUTISM** (Figure 3.53B)

- Increased number of terminal hairs in women with a male pattern of distribution (unlike hypertrichosis which is an increase in the amount of hair growth anywhere on the body)
- Androgen-dependent areas include groin, lower abdomen, breasts, chin, lateral cheeks and upper cutaneous lip
- Causes:
  - Adrenal: congenital adrenal hyperplasia, neoplasm
  - Pituitary: Cushing's disease, acromegaly, prolactin-secreting adenomas
  - Ovary: ovarian tumor, PCOS
- Other signs of virilization: deepening of voice, temporal balding, amenorrhea, acne, clitoral hypertrophy (Figure 3.53C)
- Labs: free/total testosterone, LH, FSH, DHEA-S, ± fasting glucose (if concern for PCOS)
- Treatment: spironolactone, OCP, topical eflornithine, electrolysis, laser hair removal

**Figure 3.53****A: Traction alopecia***(Courtesy of Dr. Paul Getz)***B: Hirsutism in female, cheek***(Reprint from Freedberg I, Sanchez M, eds. Current Dermatologic Diagnosis and Treatment. New York: Lippincott Williams & Wilkins; 2001)***C: Clitoral hypertrophy in child with virilizing tumor***(Reprint from Ibeiro RC, et al. Encyclopedia of Cancer. New York, NY: Springer; 2008)*

**D. HAIR SHAFT ABNORMALITIES** (Figure 3.54)**Table 3-28 Hair Shaft Abnormalities**

Entity	Clinical Findings
<b>WITH Increased Fragility</b>	
<b>‘Bubble’ hair</b>	Large, unevenly spaced ‘bubbles’ that enlarge and thin the hair cortex on microscopy; fractures occur at sites of large ‘bubbles’; due to trauma
<b>Monilethrix</b>	Beaded appearance of hair due to periodic thinning of hair shaft (like necklace or string of beads) → normal at birth, few months later with short, fragile brittle hair
<b>Trichorrhexis invaginata</b>	‘Bamboo hair’; microscopic appearance showing ball and socket or collapsible telescope Seen in Netherton’s syndrome
<b>Trichorrhexis nodosa</b>	Incomplete fracture with frayed ends resembling two paint brushes against each other Seen in Menkes disease, trichothiodystrophy, arginosuccinic aciduria, Netherton’s syndrome
<b>Trichothiodystrophy</b>	Sulfur-deficient hair with alternating light and dark bands under polarizing light
<b>Pili torti</b>	Twisting and flattening of hair fiber Seen in Björnstad syndrome, Crandall syndrome, Menkes diseases, Netherton’s syndrome
<b>Trichoschisis</b>	Clean transverse fracture of hair shaft; mechanical or acquired Seen in trichothiodystrophy
<b>WITHOUT Increased Fragility</b>	
<b>Pili annulati</b>	Alternating bright and dark bands seen in hair shaft with reflected light; light bands due to abnormal air-filled cavities with ↑ light reflex (but on microscopy appear paradoxically dark); may be sporadic or familial, may have <b>normal hair length</b> Unlike trichothiodystrophy where banding only seen with polarizing light
<b>Trichoptilosis</b>	‘Split ends’; longitudinal splits in hair shaft originating at free end, due to trauma
<b>Trichonodosis</b>	Knots develop within curly hair due to excessive combing or rustling of hair
<b>Pili recurvati</b>	‘Ingrown hairs’ or pseudofolliculitis barbae; hair exits skin surface and then re-enters causing foreign body response
<b>Rolled hairs</b>	Hair trapped in stratum corneum and subsequently appearing as dark coiled ring; may be due to friction or associated with keratosis pilaris
<b>Pili bifurcati</b>	Two hairs, which occupy same follicle, bifurcate and then rejoin; each branch has its own cuticle
<b>Pili multigemini</b>	Multiple hair shafts from one papilla; each fiber has its own inner root sheath but fibers share common outer root sheath
<b>Trichostasis spinulosa</b>	Small vellus hairs embedded within hair follicle and confused with open comedones; typically seen on nose, forehead, cheeks and neck
<b>Woolly hair</b>	Multiple abnormalities causing woolly hair; may see elliptical cross-section, axial twisting, breaks and splitting; isolated or familial Seen in Carvajal and Naxos syndrome
<b>Pili trianguli et canaliculi</b>	‘Spun glass hair’; premature keratinization of the inner root sheath; triangular cross-section with central linear groove along one side Seen in uncombable hair syndrome
<b>Acquired progressive kinking of hair</b>	Acquired curling of the scalp hair; isolated or due to trauma, medications or trichotillomania Seen in loose anagen hair syndrome
<b>Loose anagen hair</b>	Ruffled proximal cuticle, absence of root sheath
<b>Hair cast</b>	Cylindrical rings of keratin that move freely along hair shaft (likely represent shed inner root sheath); differentiate from nits (which do not freely slide off)



**Figure 3.54**

**Hair shaft abnormalities:**

**a:** Normal hair

**b:** Pili annulati

**c:** Monilethrix

**d:** Trichorrhexis invaginata

**e:** Pili torti

**f:** Trichorrhexis nodosa

**g:** Trichoptilosis

*(Reprint from Burgdorf WH, Plewig G, Landthaler M, Wolff HH, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009)*

### 3.14 NEUROPSYCHOCUTANEOUS DISORDERS

**Table 3-29 Neuropsychocutaneous Disorders**

Entity	Clinical Findings	Treatment
<b>Delusions of parasitosis</b>	Fixed false belief of being infested with parasites; imaginary parasites typically reported as 'bugs' crawling under skin (formication)  Need to distinguish from substance-induced formication	Treatment: antipsychotic medication such as <b>pimozide</b> (side effects include extrapyramidal side effects and <b>prolonged QT interval</b> ) or risperidone
<b>Body dysmorphic disorder</b>	Excessive concern over perceived defect in body image with ↑↑ time spent checking for imperfections	Spectrum ranges from obsessive to delusional thinking Treatment: SSRIs if OCD variant, antipsychotics if delusional variant
<b>Dermatitis artefacta</b> (Factitial dermatitis)	Deliberate creation of self-inflicted cutaneous lesions; lesion morphology variable but often with bizarre geometric shapes with sharp margins  Typically lesions created to satisfy an unconscious psychological or emotional need (secondary gain)	Treatment: topical medication to help with healing; ± antidepressants, antipsychotic or antianxiety medications
<b>Neurotic excoriations</b>	Unconscious to uncontrollable picking (either at pre-existing skin lesions or de novo); excoriations with irregular borders	Treatment: treat any underlying cutaneous disease (i.e. acne), antihistamines for pruritus (i.e. doxepin), ± SSRIs
<b>Gardner-Diamond syndrome</b>	Factitial disorder; <b>painful swollen ecchymoses</b> at sites of trauma, often in women with an underlying psychiatric illness	Treatment: difficult



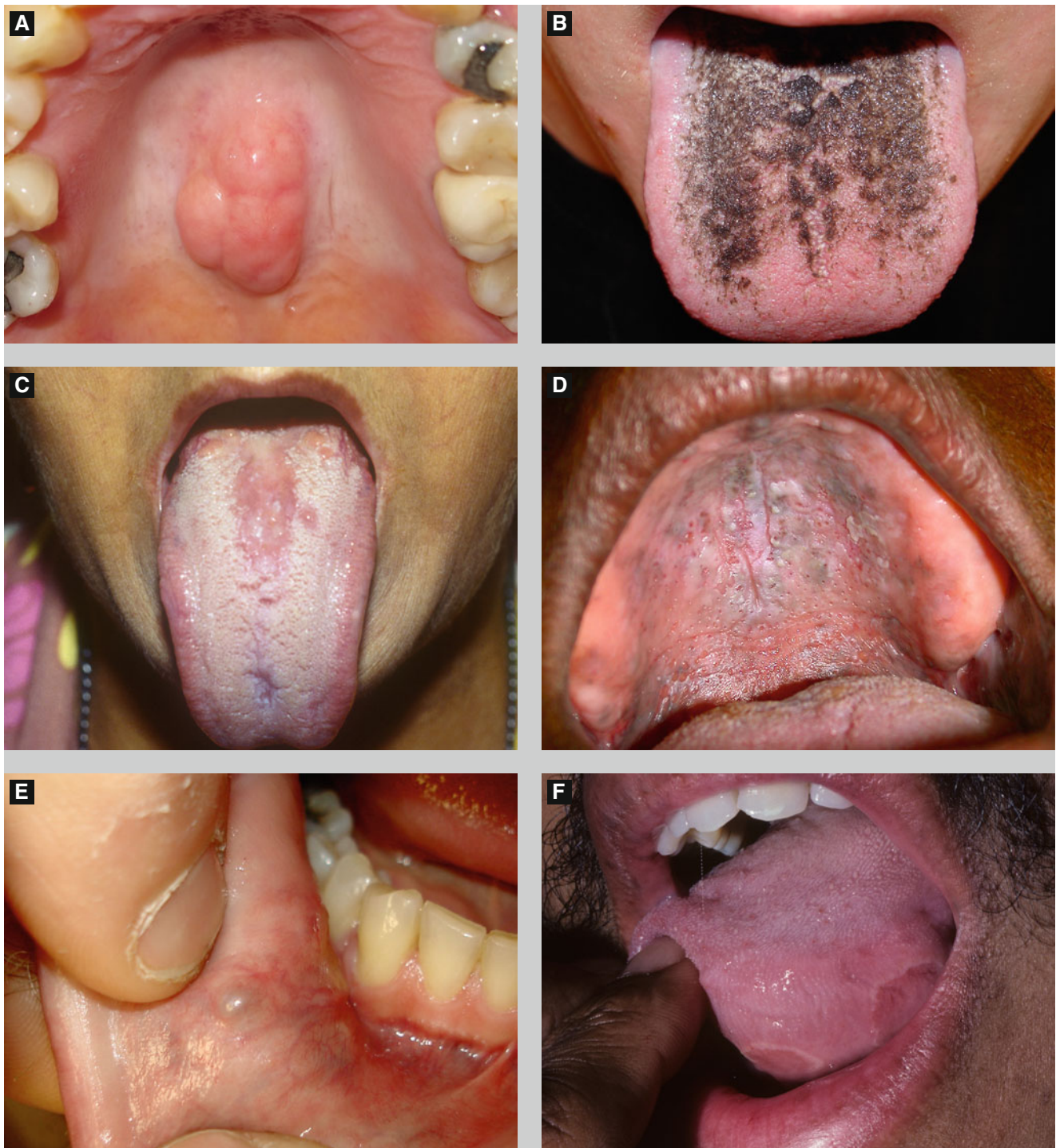
### 3.15 ORAL DISEASES

**Table 3-30 Oral Diseases**

Entity	Clinical Findings	Associations
<b>Normal variations in anatomy</b>		
<b>Fordyce granules</b>	Multiple 1–2 mm yellow papules on buccal mucosa and upper lip vermillion	Ectopic sebaceous glands, normal variation of anatomy
<b>Torus</b> (Figure 3.55A)	Bony outgrowth along hard palate or mandibular area (palatal/mandibular tori)	5–10% of the population
<b>Reactive process/injury</b>		
<b>Geographic tongue</b> (Figure 3.55F)	Well-demarcated erythema with whitish rim typically involving dorsal tongue	↑ Frequency with psoriasis
<b>Fissured tongue</b> (Scrotal tongue)	Nonpainful furrows on dorsum of tongue with ‘corrugated’ appearance	May be associated with Melkersson-Rosenthal syndrome
<b>Hairy tongue</b> (Black hairy tongue) (Figure 3.55B)	Yellow to brown-black elongated and hypertrophic papillae with hair-like projections on dorsum of tongue	Due to keratin accumulation; association with smoking, poor hygiene, or antibiotic use
<b>Leukoedema</b>	Diffuse grey-white surface along buccal mucosa	Benign, disappears with stretching of affected area
<b>Desquamative gingivitis</b>	Diffuse gingival erythema with erosions, ± mucosal sloughing	General term for findings in many vesiculoerosive diseases
<b>Morsicatio buccarum</b>	Shaggy white plaque on buccal mucosa	Chronic irritation from biting
<b>Irritant contact stomatitis</b>	White wrinkled necrotic plaque at site of contact with subsequent desquamation	Self-limited; often due to aspirin
<b>Allergic contact stomatitis</b>	Shaggy white hyperkeratotic areas on buccal mucosa resembling oral LP	Dental amalgam and cinnamon may cause lichenoid changes
<b>Amalgam tattoo</b>	Black or bluish-black pigmented macule typically over buccal vestibule	After tooth extraction, amalgam may incorporate in wound
<b>Nicotine stomatitis</b> (Figure 3.55D)	Umbilicated papules with central red depression over hard palate/soft palate	Inflamed palatal mucous salivary glands due to nicotine
<b>Orofacial granulomatosis</b> (Cheilitis granulomatosa)	Persistent, non-tender enlargement of lips (upper or lower lip) and/or face  <b>Melkersson-Rosenthal:</b> facial nerve palsy, fissured tongue, granulomatous cheilitis	Associated with Melkersson-Rosenthal syndrome
<b>Aphthous stomatitis</b>	Round to oval painful shallow ulcers with creamy-white base and red halo	Three forms: minor, major and herpetiform
<b>Salivary gland disease</b>		
<b>Mucocele</b> (Figure 3.55E)	Soft, blue, translucent cyst (superficial) or mucosa-colored firm nodule (deep)	Due to obstruction or rupture of minor salivary glands
<b>Cheilitis glandularis</b>	Pinpoint red macules on lower lip mucosa, ± enlargement of lower lip	Dilated/inflamed minor salivary glands; treat w/ vermillionectomy
<b>Xerostomia</b>	Absent/reduced salivary secretion causing dryness of mouth	Side effect of medications, autoimmune disease, XRT, etc.
<b>Bacterial, viral or fungal infections</b>		
<b>Necrotizing ulcerative gingivitis</b>	Hemorrhagic painful gingiva with punched out lesions and foul odor	Associated with many oral bacterial pathogens
<b>Median rhomboid glossitis</b> (Figure 3.55C)	Diamond or oval-shaped erythematous smooth plaque on posterior dorsal tongue	Asymptomatic, may resolve on own; likely due to <i>C. albicans</i>
<b>Angular cheilitis</b> (Perleche) (Figure 3.56B)	Erythema, maceration and fissuring at the lip commissures	Vitamin deficiency, candidal infection, irritant dermatitis
<b>Glossitis</b>	Atrophic, smooth red glistening tongue	Candidiasis or vitamin deficiency

Table 3-30 Oral Diseases (cont'd)

Entity	Clinical Findings	Associations
<b>Thrush</b>	Loosely adherent white patches or plaques on mucosal surfaces	Due to candidal infection
<b>Heck's disease</b> (Focal epithelial hyperplasia)	Pink to white soft papules/plaques with cobblestone appearance over lips, buccal mucosa and/or lateral sides of tongue	Infection of mucosa by <b>HPV</b> types <b>13</b> and <b>32</b>
<b>Primary herpetic gingivostomatitis</b>	Painful vesicles and ulcers; typically with diffuse gingival involvement	Primary HSV infection
<b>Benign, premalignant and malignant lesions</b>		
<b>White sponge nevus</b>	White, thickened spongy plaques typically over buccal mucosa bilaterally, ± labial mucosa, tongue, floor of mouth	Rare, autosomal dominant, present at birth or shortly after; mutation in <b>keratin 4</b> and <b>13</b>
<b>Verruciform xanthoma</b>	Soft, sessile plaques typically over gingiva, alveolar mucosa and hard palate	No associated lipid abnormality <b>Foamy lipid-laden cells</b> req'd for diagnosis
<b>Mucosal neuromas</b>	Painless soft or rubbery papules/nodules affecting mainly lips and tongue	<b>MEN 2B (type 3)</b>
<b>Granular cell tumor</b>	Solitary firm, sessile nodule typically on tongue; asymptomatic	30% confined to tongue (rest arising on head and neck)
<b>Oral fibrous histiocytoma</b> (Figure 3.56C)	Solitary, pink smooth nodule typically on buccal mucosa, tongue, gingiva or lip	Asymptomatic
<b>Leukoplakia</b>	White plaque on floor of the mouth and lateral/ventral tongue, soft palate	Most common premalignant oral lesion
<b>Erythroplakia</b>	Flat or slightly erythematous sharply marginated patch or plaque	90% carcinoma in situ or invasive at time of biopsy
<b>Actinic cheilitis</b> (Figure 3.56D)	Blurring of vermillion border, change in texture/color of lip, ± scale, ulceration	Precancerous; typically diffuse
<b>SCC</b> (Figure 3.56E, F)	Ulcer, indurated plaque or exophytic mass typically over <b>lateral/ventral tongue and floor of mouth</b>	Strongly associated with tobacco, alcohol, HPV infection, and chewing betel nut
<b>Verrucous carcinoma</b>	Slow growing exophytic verrucous or papillary white plaque	Distinct subtype of SCC, locally aggressive; HPV type 16 and 18
<b>Miscellaneous</b>		
<b>Oral Crohn's disease</b>	Linear fissures and ulcers of vestibule, cobblestone lesions on buccal mucosa	Oral lesions respond to therapy for bowel disease
<b>Pyostomatitis vegetans</b> (Figure 3.56A)	'Snail-track' creamy-yellow tiny pustules arranged in linear, serpentine fashion against erythematous background	Associated with IBD (Crohn's, UC), similarities to oral variant of pyoderma gangrenosum
<b>Gingival hyperplasia</b>	Hyperplasia of gingiva with interdental papillae being affected first	Seen in phenytoin, calcium channel blockers, cyclosporine



**Figure 3.55**

**A: Torus on hard palate**

**B: Black hairy tongue**

**C: Median rhomboid glossitis**

(Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases*. New York, NY: Springer; 2008)

**D: Nicotinic stomatitis**

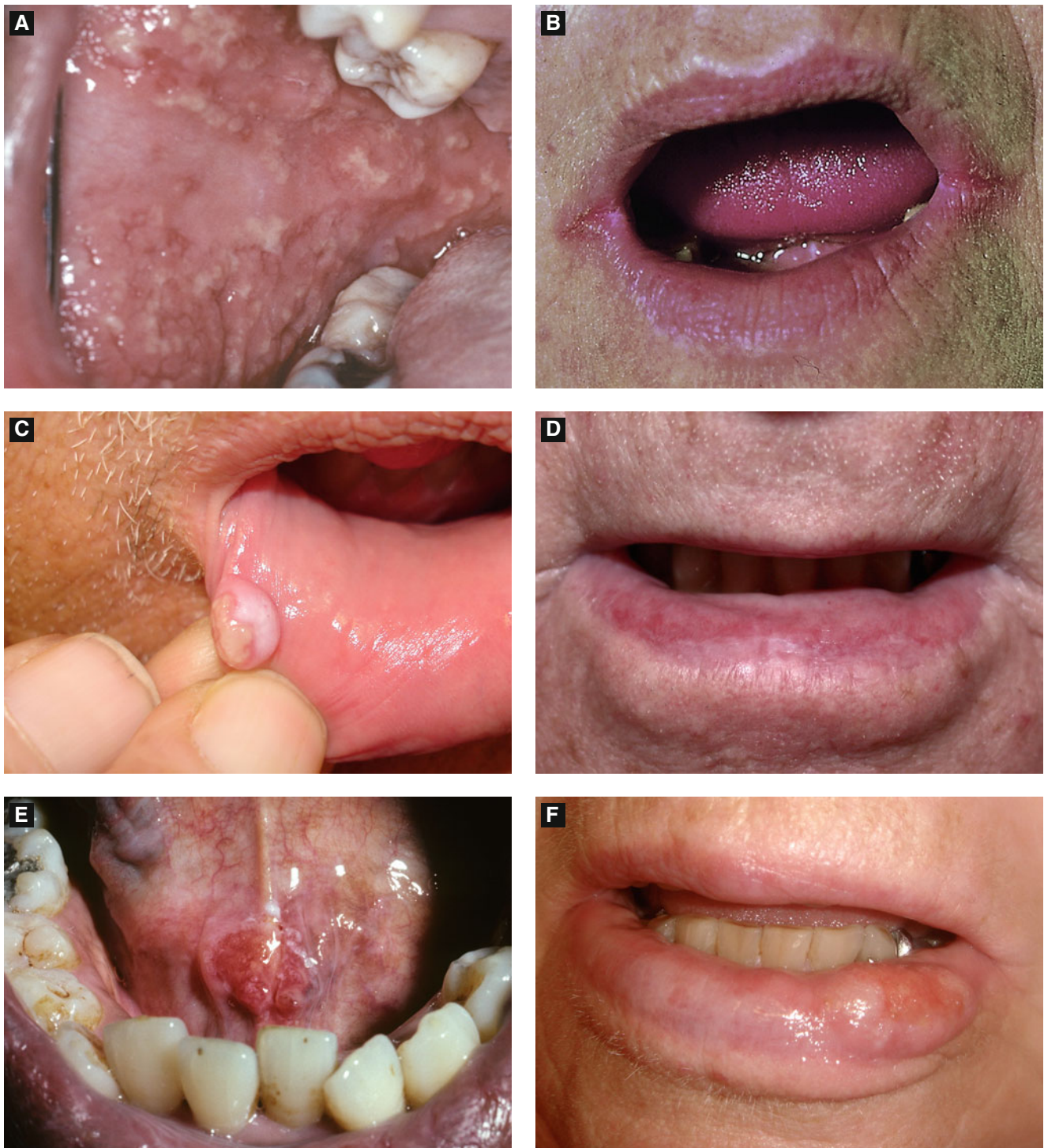
(Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases*. New York, NY: Springer; 2008)

**E: Mucocoele**

**F: Geographic tongue**

(Courtesy of Dr. Paul Getz)





**Figure 3.56**

**A: Pyostomatitis vegetans**

(Reprint from Nevill B. *Update on Current Trends in Oral and Maxillofacial Pathology. Head and Neck Pathology. Sep 2007; 1(1): 75–80*)

**B: Angular cheilitis**

(Reprint from Trueb R, Tobin D, eds. *Aging Hair. London: Springer; 2010*)

**C: Oral fibrous histiocytoma**

**D: Actinic cheilitis**

(Reprint from Norman R, ed. *Diagnosis of Aging Skin Diseases. New York, NY: Springer; 2008*)

**E: SCC, oral**

(Courtesy of Dr. Paul Getz)

**F: SCC, lower lip**



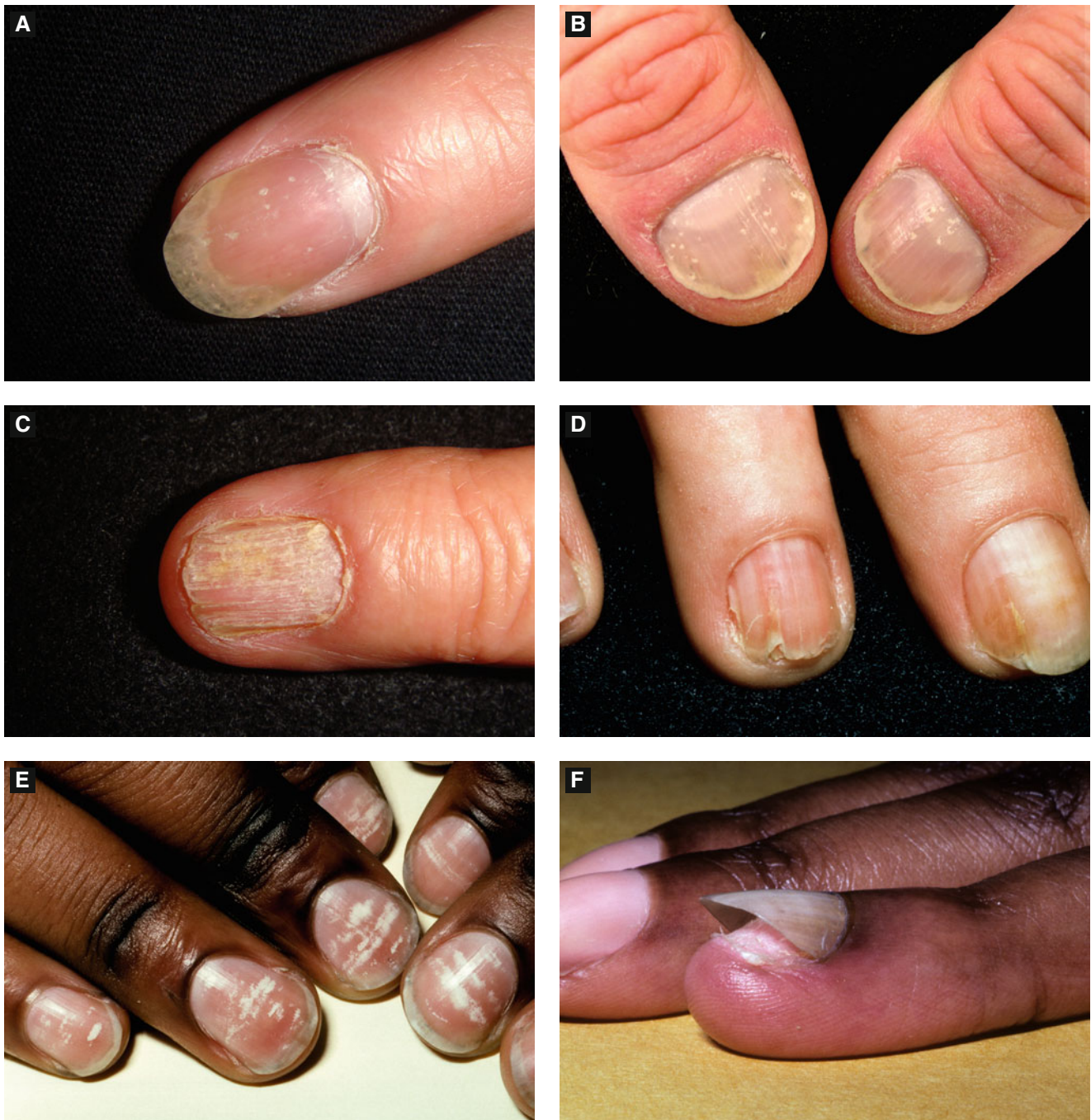
### 3.16 NAIL DISEASES

**Table 3-31 Nail Disorders**

Entity	Clinical Findings	Associated Diseases
<b>Nail matrix</b>		
<b>Beau's lines</b> (Figure 3.58D)	Transverse depression in nail plate surface	Severe systemic event (all nails) or trauma/disease of matrix (single nail)
<b>Hapalonychia</b>	Soft nail plate	
<b>Koilonychia</b> (Spoon nails)	Thin, concave nails with eversion of free nail edge	Hereditary, physiologic (children), iron deficiency, thyroid abnormality
<b>Leukonychia, diffuse</b>	Opaque or completely white nail plate	Chemotherapy, white superficial onychomycosis, congenital disease
<b>Leukonychia, punctate</b>	White macules on nail plate	Psoriasis (PSO), trauma to matrix
<b>Leukonychia, transverse</b> (striate) (Figure 3.57E)	Narrow white transverse lines along nail plate	Trauma to matrix
<b>Mee's lines</b>	Transverse lines of entire nail breadth in all nails	Arsenic poisoning, trauma, medications, severe illness, PSO (flare)
<b>Onychomadesis</b> (Nail shedding)	Detachment of nail plate from proximal nail fold (PNF) → shedding of nail	Traumatic, medications (i.e. chemo), drug reaction (i.e. TEN), autoimmune diseases, systemic illness
<b>Onychorrhexis</b> (Figure 3.58E)	Longitudinal ridging, ± fissuring of plate	Lichen planus, chronic trauma, repeated wet/dry cycles, <b>normal with aging</b>
<b>Pitting</b> (Figure 3.57A)	Punctate depressions of nail plate surface Elkonyxis: large 2-mm pits	Psoriasis (PSO), alopecia areata, eczema
<b>Red lunula</b>	Pink to red spots within lunula	Alopecia areata, rheumatoid arthritis, LE, CHF, CO poisoning
<b>Trachyonychia</b> (20 nail dystrophy) (Figure 3.57C)	Rough, thinned nails with longitudinal ridging	Alopecia areata, lichen planus (LP), PSO, eczema
<b>Nail bed</b>		
<b>Apparent leukonychia</b>	White discoloration (fades with pressure); nail plate looks white but normal color	Drugs (i.e. chemo agents) or systemic disease
<b>Oil spots</b> (Figure 3.57B)	Brown spots under nail plate	PSO
<b>Onycholysis</b> (Figure 3.57F)	White discoloration at distal end where nail plate separated from bed	PSO, trauma, onychomycosis, medications (TCN, NSAID, PUVA), tumors, systemic diseases (hyperthyroidism), pregnancy
<b>Splinter hemorrhages</b> (Figure 3.59A, B)	Thin, longitudinal red-brown lines along nail plate	Trauma, PSO, fungal (distal); endocarditis, vasculitis, trichinosis (proximal)
<b>Nail color</b>		
<b>Half and half nails</b> (Lindsay's nails) (Figure 3.59C)	Proximal ½ with white zone, distal ½ with red-brown zone	Chronic renal disease
<b>Hutchinson's sign</b>	Periungual black discoloration	Melanoma
<b>Muehrcke's bands</b>	Transverse white bands parallel to lunula	Hypoalbuminemia, chemotherapy
<b>Melanonychia</b>	Partial or diffuse Common in darkly pigmented skin types	Drugs, melanoma, Laugier-Hunziker
<b>Longitudinal melanonychia</b> (Melanonychia striata) (Figure 3.58F)	Vertical brown-black band (proximal to distal margin)	Nevus, lentigo, drugs, trauma, melanoma
<b>Terry's nails</b> (Figure 3.59D)	Proximal 2/3 white nail color, distal 1/3 brown-pink band	Cirrhosis, hypoalbuminemia, diabetes, cardiac disease

**Table 3-31 Nail Disorders (cont'd)**

Entity	Clinical Findings	Associated Diseases
<b>Others</b>		
<b>Absent lunula</b>	No visible lunula	Yellow nail syndrome, renal failure, trauma
<b>Anonychia</b>	Absence of nail	Nail patella syndrome, COIF, (Congenital Onychodysplasia of the Index Finger) scarring
<b>Blue lunula</b>	Blue discoloration of lunula	Wilson's, drugs, PUVA, argyria, etc.
<b>Brachyonychia</b>	Short, wide nails	Rubinstein-Taybi syndrome, PSO
<b>Clubbing</b>	↑ Nail curvature w/ bulbous growth of tip of digit	Chronic pulmonary disease, idiopathic, familial, systemic disease
<b>Dolichonychia</b>	Long nails	Marfan's, Ehlers Danlos, etc.
<b>Dorsal pterygium</b> (Figure 3.58C)	Wing-like growth fusing PNF with nail bed/matrix	<b>Lichen planus</b> , epidermal bullosa, TEN, GVHD, TEN, cicatricial pemphigoid
<b>Habit tic deformity</b> (Figure 3.58A)	Parallel horizontal grooves	Caused by repetitive trauma to cuticle
<b>Macronychia</b>	Large nails	Congenital abnormality
<b>Median canaliform dystrophy</b> (Figure 3.58B)	Inverted 'fir tree' (oblique lines from midline defect)	Idiopathic or inherited
<b>Micronychia</b>	Small nails	Congenital defect (i.e. COIF)
<b>Onychauxis</b>	Hypertrophic nail plate	May be due to chronic trauma
<b>Onychoatrophy</b>	Reduction in size and thickness of nail plate	LP, vascular insufficiency, systemic disorders, medications
<b>Onychocryptosis</b>	Ingrown nail	
<b>Onychogryphosis</b>	Grossly thickened and long nail, resembling claw	Inability to cut toenails, long-term pressure (i.e. shoes), neglect
<b>Onychophagia</b>	Nail biting	
<b>Onychoschizia</b> (Lamellar nail splitting)	Distal lamellar separation into horizontal layers	Repeated wet and dry cycles, trauma, systemic disease and medications
<b>Onychotillomania</b>	Chronic picking of nail	
<b>Pachyonychia</b>	Thickened nails	Pachyonychia congenita
<b>Pincer nails</b>	Overcurvature lateral portion	Pressure (ill-fitting shoes), hereditary
<b>Platyonychia</b>	Flat nail	Inherited or acquired
<b>Racket nails</b>	Distal phalanx short/wide	Form of brachyonychia
<b>Subungual exostosis</b> (Figure 3.59E, F)	Painful, bony subungual growth elevating nail plate	X-ray confirms bony exostosis
<b>Triangular lunula</b>	Triangular shape of lunula	Nail-patella syndrome
<b>Ventral pterygium</b> (Pterygium inversum unguis)	Fusion of hyponychium to distal nail plate	Familial, trauma, <b>systemic sclerosis</b> , lupus erythematosus
<b>Yellow nails</b>	Yellow color to nail plate	Yellow nail syndrome, drugs, chronic enamel  <b>Yellow nail syndrome:</b> pulmonary disorder + lymphedema + yellow, slow growing nails with absent lunulae
<b>V-shaped nicking</b> (Figure 3.57D)	V-shaped nick at free margin	Darier disease



**Figure 3.57**

**A: Pitting**

**B: Pitting, 'oil spots' and onycholysis (psoriatic nail)**

**C: Trachyonychia**

**D: Darier nail (v-shaped nicking)**

*(Courtesy of Dr. Paul Getz)*

**E: Leukonychia striata**

*(Courtesy of Dr. Paul Getz)*

**F: Onycholysis**

*(Courtesy of Dr. Paul Getz)*





**Figure 3.58**

**A:** Habit tic deformity

**B:** Median nail dystrophy

**C:** Dorsal pterygium in lichen planus

(Reprint from Tosti A, Ralph DC, Piraccini BM, Iorizzo M. *Color Atlas of Nails*. Berlin: Springer; 2010)

**D:** Beau's lines (Courtesy of Dr. Paul Getz)

**E:** Onychorrhexis (longitudinal ridging)

**F:** Melanonychia striata

(Courtesy of Dr. Sophie M. Worobec)





**Figure 3.59**

**A: Splinter hemorrhage**

*(Courtesy of Dr. Paul Getz)*

**B: Splinter hemorrhage**

**C: Half-half nails**

**D: Terry's nails**

*(Reprint from Tosti A, Ralph DC, Piraccini BM, Iorizzo M. Color Atlas of Nails. Berlin; Springer; 2010)*

**E: Subungual exostosis**

*(Courtesy of Dr. Paul Getz)*

**F: Subungual exostosis**

*(Courtesy of Dr. Paul Getz)*

### 3.17 PHOTODERMATOSES

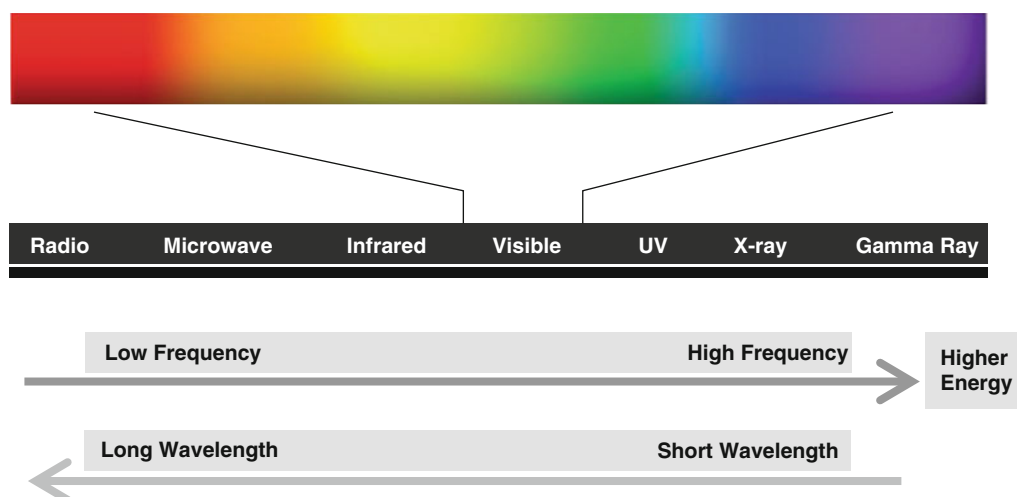
#### A. EM SPECTRUM AND BIOLOGICAL EFFECTS

##### Electromagnetic (EM) Spectrum (Figure 3.60)

- Classification based on wave frequency and includes (starting with lowest frequency/energy) radio waves, micro-waves, infrared radiation (IR), visible light (VL), ultraviolet light (UVL), X-rays and gamma rays (latter two known as ionizing radiation)
- Energy of photon is proportional to frequency of radiation and inversely proportional to wavelength; thus, energy increases as wavelength decreases and frequency increases
- Chromophores of epidermis include nucleic acid, protein, urocanic acid and melanin; chromophores of dermis include hemoglobin and porphyrins
- **Absorption spectrum:** portion of EM spectrum absorbed by particular light-absorbing molecule or chromophore (i.e. wavelengths absorbed by porphyrins)
- **Action spectrum:** portion of EM spectrum producing particular biologic effect (i.e. wavelength of radiation causing erythema)
- **Minimal erythema dose (MED):** minimal amount of particular wavelength of light capable of inducing erythema
- **Ultraviolet light (UVL):** (Table 3-32)
  - Non-ionizing type of radiation; invisible to human eye; classified into UVA (315–400 nm), UVB (290–315 nm), and UVC (200–290 nm)
  - Depth of penetration of UVL depends on wavelength: longer wavelength with deeper penetration (UVA penetrates deeper than UVB); practically all of UVC absorbed by ozone layer

##### UVR-Induced Changes

- High-frequency UVR results in DNA damage (mutations) and immunosuppression (local/systemic) – both steps key to photocarcinogenesis
- DNA damage
  - DNA considered chromophore for most biological effects from UVB and UVC
  - Direct DNA damage via photoproducts, which are dimers formed by covalent bonding between adjacent pyrimidines (cytosine or thymine) in same polynucleotide chain; if dimers unrepaired or incorrectly repaired, results in mutation specific to UVB → cytosine changed to thymine (C to T), referred to as signature of UVB effect on DNA
  - Cyclobutane-pyrimide dimers (CPD): most common DNA photoproduct; most frequent thymine-thymine (T-T) > C-T > T-C and C-C
  - 6,4-photoproduct: noncyclobutane dipyrimidine DNA photoproduct
  - Indirect DNA damage from UVA likely via formation of reactive oxygen species (ROS)
  - Immunosuppression: ↓ number of Langerhans cells, modification of antigen-presenting cell capacity, release of immunosuppressive cytokines (IL1, IL10, TNF $\alpha$ , etc.)



**Figure 3.60**  
Electromagnetic spectrum

**Table 3-32 Comparison of UVA and UVB**

Factors	UVA	UVB
<b>Wavelength</b>	315–400 nm (UVA1: 340–400, UVA2: 315–340)	290–315 nm
<b>Solar erythema</b> (sunburn)	Minor role; <b>immediate erythema</b> and distinct delayed erythema (6–24 h after exposure)	<b>Major role</b> ; 6–24 h after exposure; <b>UVB 1000× more erythemogenic</b> than UVA; produces apoptotic ‘sunburn’ cell
<b>Skin penetration</b>	Epidermis through deep dermis (epidermal/dermal chromophores)	Epidermis only (fraction reaches upper dermis); causes epidermal thickening
<b>Darkening</b>	<b>Immediate pigment darkening</b> (hrs after exposure; due to <b>oxidation</b> of <b>pre-existing melanin</b> , redistribution of melanosomes)	<b>Delayed melanogenesis</b> (48–72 h after exposure) due to ↑ # melanocytes, ↑ #/size melanosomes, ↑ synthesis/transfer melanin; provides photoprotection
<b>Drug-induced photosensitivity</b>	<b>Major contributor</b>	Minor role
<b>Carcinogenesis</b>	Minor role; ROS production	<b>Major role</b> : mutations in keratinocyte DNA (CPDs) and immunosuppression
<b>Vit D3 production</b>	No	Yes
<b>Glass penetration</b>	<b>Yes</b> (penetrates window glass)	No
<b>Miscellaneous</b>	95% of UVR reaching earth’s surface, phytophotodermatitis	NBUVB 313 nm; Wood’s light ~365 nm (nickel oxide doped glass)

**UVA:** Drug-induced photosensitivity, photoaging, immediate pigment darkening, erythema

**UVB:** Photocarcinogenesis, solar erythema, delayed pigment darkening, vitamin D3 synthesis

- DNA repair mechanisms
  - Photoproducts repaired by nucleotide excision repair (NER) pathway (includes seven genetic complementation groups and variant form)
  - Post replication repair: damaged DNA ignored instead of repaired; replaced during replication but likely not very accurate

## B. ENDOGENOUS PHOTODERMATOSES

### Polymorphous Light Eruption (PMLE)

- Acquired photo-induced disease presenting in mainly second or third decade; often seen in spring or early summer; most common form of idiopathic photodermatitis
- Likely due to delayed hypersensitivity reaction to endogenous photo-induced antigen
- Presents typically with patchy erythematous papules, plaques or vesicles within minutes to hours (sometimes days) of UV exposure in sun-exposed sites; improves as summer progresses (natural ‘hardening’)
- **Juvenile spring eruption:** PMLE variant in boys or young men with involvement of ears (helices) typically
- Histology: superficial and deep lymphocytic perivascular infiltrate with striking papillary dermal edema
- Treatment: topical or oral corticosteroid; overall treatment includes high SPF and restriction of UVR exposure, low dose NBUVB, PUVA or antimalarial

### Actinic Prurigo (PMLE of Native Americans)

- Similar to PMLE but seen mainly in native American children; begins before age 10 in most cases (earlier than PMLE) and typically worse in spring and summer
- Presents with erythematous edematous plaques with ensuing hemorrhagic crust and excoriations on exposed surfaces; pitted or minute linear scars left after lesions heal; associated cheilitis and conjunctivitis; improves/resolves in adolescence
- Histology: epidermal spongiosis with dermal edema, perivascular mononuclear cell infiltrate
- Treatment: photoprotection and topical corticosteroid, thalidomide (only effective systemic agent)

### Hydroa Vacciniforme

- Uncommon photo-induced scarring disorder seen in early childhood and may resolve by adolescence or young adulthood; worse in spring/summer and in some cases may be associated with latent EBV infection; hydroa-vacciniforme-like skin changes with a specific type of EBV-associated lymphoma
- Presents with erythematous papules and plaques on sun-exposed sites within hours of sun exposure → evolve into hemorrhagic bullae with crusting → heal with varioliform scars
- Histology: early spongiosis, focal intraepidermal vesicles, keratinocyte degeneration, epidermal/upper dermal necrosis
- Treatment: refractory to treatment, photoprotection

### Solar Urticaria

- Rare photodermatosis causing urticaria minutes after sun exposure; little tendency toward resolution
- Presents with burning and erythema followed by urticaria immediately after sun exposure; severe attacks may be associated with anaphylactic-type response with lightheadedness, nausea, syncope and bronchospasm
- Histology: mild dermal edema with perivascular neutrophilic and eosinophilic infiltrate
- Treatment: photoprotection, non-sedating histamine and sometimes topical corticosteroids, graduated UV exposure

### Chronic Actinic Dermatitis (Actinic Reticuloid: severe clinical variant)

- Persistent UVR-evoked eczema of exposed areas (lesser extent non exposed areas) affecting older men during summer time
- Presents with pruritic, patchy or confluent areas of eczematous change, lichenification or erythematous infiltration; typically worse in summer
- Histology: changes vary from psoriasiform hyperplasia to interface dermatitis to atrophy
- Treatment: photoprotection, topical corticosteroid, low dose NBUVB or PUVA, azathioprine, cyclosporine

## C. EXOGENOUS PHOTODERMATOSES

- Reaction due to combination of light (typically UVA) and photosensitizing chemical
- Phototoxic (direct tissue damage) vs. photoallergic drug reaction; other light-related drug reactions include pseudoporphyria, lichenoid or SCLE-like reactions (see Chap. 7)

### Phototoxic Dermatitis

- Common reaction resembling sunburn with rapid onset (minutes to hours); requires photosensitizer which magnifies effect of sunlight and damages keratinocytes
- Occurs in most people if exposed to sufficient amounts of light and drug; typically only in sun-exposed sites
- Presents with erythema in sun-exposed sites resembling sunburn, may have exaggerated postinflammatory hyperpigmentation, ± onycholysis
- Treatment: photoprotection and removal of photosensitizer

### Photoallergic Dermatitis

- Less common reaction resembling allergic contact dermatitis with delayed onset (24–72 h); form of delayed type hypersensitivity reaction due to allergen either taken systemically or applied topically
- Prior exposure to allergen needed, and once sensitized any form of exposure may cause eruption; may see cross-reactivity unlike phototoxic eruptions
- Presents with pruritus in sun-exposed areas with erythematous patches and papules, ± bullae; chronic exposure may cause lichenification
- Treatment: allergen avoidance and photoprotection



**Table 3-33 Drugs Causing Phototoxic and Photoallergic Reactions**

Phototoxic		Photoallergic	
Tetracycline (demeclocycline > doxycycline > TCN)	Phenothiazines (chlorpromazine, promethazine)	Phenothiazines (chlorpromazine, promethazine)	Sulfonylureas (glipizide, glyburide)
Fluoroquinolone	Furosemide	Musk ambrette	Sunscreen (PABA, cinnamates, <b>benzophenones</b> , salicylates)
NSAIDs	Hydrochlorothiazide	Hydrochlorothiazide	Most common allergen in sunscreen (includes oxybenzone)
Furocoumarins	Statins	Statins	
Alprazolam	Sulfonamides	Sulfonamides	
Oral retinoids	Diltiazem	Dapsone	
Amiodarone	Griseofulvin	Griseofulvin	
PABA	Quinidine	Quinidine	

**Phytophotodermatitis** (Table 3-34)

- Form of phototoxic dermatitis due to plants containing phototoxic chemicals (especially furocoumarins) via either ingestion or skin contact
- Contact with plant juice may cause burning and bullae when sites exposed to sunlight
- Treatment: avoid photosensitizer, topical corticosteroid

**Table 3-34 Plants Causing Phytophotodermatitis**

Family Name	Members
Apiaceae (Umbelliferae)	Angelica, parsley, hogweed, celery, parsnip, fennel, wild rhubarb, wild chervil
Rutaceae	Lime, lemon, grapefruit, rue, orange, burning bush, mokihana (lei flowers)
Moraceae	Fig tree
	Clusiaceae (family): St. John's wort

## D. CHEMICALS BLOCKING UVR

**Table 3-35 Sunscreen Agents**

**Salicylates:** octisalate, homosalate, trolamine salicylate

UVA	UVB
Avobenzone, benzophenones (oxybenzone), ecamsule (Mexoryl SX), meradimate	PABA, padimate O, cinnamates, salicylates, octocrylene, ensulizole, Mexoryl XL (drometrizole trisiloxane)

**UVA & UVB blockers:** Mexoryl XL, oxybenzone, titanium dioxide and zinc oxide

**Table 3-36 Fitzpatrick Skin Types**

Type	Reaction to Sun Exposure	
Type I	Always burns	Never tans
Type II	Usually burns	Rarely tans
<b>Type III</b>	<b>Rarely burns</b>	<b>Usually tans</b>
Type IV	Never burns	Always tans
Type V, VI	Never burns	Always tans

## E. MISCELLANEOUS

### Fluoroscopy-Induced Chronic Radiation Dermatitis (FICRD)

- Skin injury from exposure to ionizing radiation (X-rays) in form of fluoroscopy; ↑ incidence due to increased number and length of procedures involving fluoroscopy (including angioplasty, cardiac catheter ablation, stent placement, vascular embolization, etc.)
- Skin changes may appear within 7–14 days after exposure (acute) or may manifest several months to years after exposure (chronic)
- Certain threshold must be attained (via single or cumulative doses) to cause skin injury
- May initially present with erythema, pain, burning or pruritus; typically affected area turns atrophic with sclerosis, telangiectasias, discoloration or ulceration, ± non-melanoma skin cancer (NMSC) within sites
- Characteristic location left or right scapular or subscapular region, right midaxillary trunk, midback or right anterolateral chest with often geometric or angulated shape
- Histology: findings consistent with chronic radiation dermatitis
- Treatment: topical or IL corticosteroid, surgical excision for ulcerated/sclerotic lesions

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# 4

## Infectious Diseases

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## 4.1 VIRAL INFECTIONS

### A. HUMAN HERPESVIRUSES (HHV)

- Eight types of HHVs:

HHV1 → HSV1	HHV5 → CMV
HHV2 → HSV2	HHV6
HHV3 → VZV	HHV7
HHV4 → EBV	HHV8 → KSHV

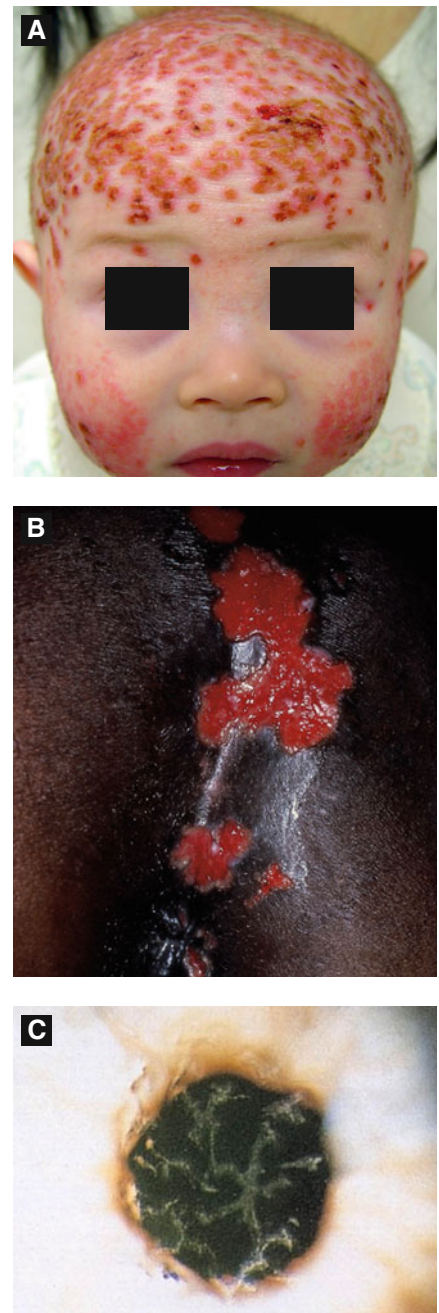
#### Herpes Simplex Virus 1 and 2 (HHV1, HHV2) (Figure 4.1A–C)

- Neurotropic virus which hides in the dorsal root ganglion until reactivation
- HSV-1 associated more with orolabial herpes, HSV-2 with genital herpes
- Primary infections:
  - Primary herpetic gingivostomatitis:** typically in children; presents with abrupt onset of striking gingivitis (erythematous, friable gingiva), painful vesicles clustered on oral mucosa, tongue, lips, and/or perioral skin → vesicles rupture, leaving small ulcers with characteristic gray base; ± pharyngitis, tonsillitis, difficult to eat and swallow, enlarged lymph nodes, fever, and anorexia
  - Primary genital infection:** more severe and prolonged than recurrent infection, presents with constitutional symptoms and painful grouped vesicles in genitalia → progress to pustules, crusting and exquisitely tender ulcers, ± painful lymphadenopathy, cervicitis, urethritis, proctitis
- Recurrent infections:
  - Herpes labialis:** most common HSV-1 manifestation triggered by pyrexia, stress, sunburn, and/or trauma; prodrome (pain, burning, tingling) may precede eruption; grouped vesicles on erythematous base which typically evolve into pustules and then painful ulcers (often involving vermillion border)
  - Genital herpes:** ± prodrome followed by grouped vesicles → pustules → ulceration
- Other types of infections:
  - Herpes gladiatorum:** HSV primary infection primarily noted in wrestlers and involving extramucosal sites typically over face, neck, or arms
  - Herpetic whitlow:** painful primary herpetic infection of hand (typically distal phalanx) resulting in exquisite pain and swelling of finger with characteristic vesicular lesions; more common in health-care workers or caregivers



**Figure 4.1**  
**A: Recurrent HSV infection**  
 (Courtesy of Dr. Paul Getz)  
**B: Primary genital HSV**  
 (Courtesy of Dr. Paul Getz)  
**C: Primary genital HSV**

- **Eczema herpeticum** (Kaposi varicelliform eruption): rare disseminated form of HSV mainly seen with atopic dermatitis (also Darier disease, Hailey–Hailey, etc.); presents as monomorphic umbilicated vesiculopustules or punched out ulcerations with hemorrhagic crust; may progress to life-threatening infection (Figure 4.2A)
- **Herpes-associated erythema multiforme (HAEM)**: self-limited eruption associated with HSV infection; presents with typical concentric target plaques; begins on extremities and spreads centripetally,  $\pm$  mucosal involvement
- **HSV encephalitis**: dormant HSV in trigeminal ganglion  $\rightarrow$  travels retrograde to the brain, targets temporal region of brain, 70% mortality if untreated
- **HSV folliculitis**: rare manifestation
- **Chronic ulcerative HSV**: presents mainly in immunocompromised patients as persistent ulcers involving perianal/buttock area and can be pustular, exophytic, or verrucous as well (Figure 4.2B)
- **Keratoconjunctivitis**: can be primary or recurrence, latter typically presents branching dendritic corneal ulcerations (seen with fluorescein stain), can lead to scarring and blindness (Figure 4.2C)
- **Diagnosis:**
  - Tzanck smear shows multinucleated epithelial giant cells (fusion of infected keratinocytes) – does not differentiate between HSV and VZV
  - Viral culture or direct fluorescent antibody (DFA)
  - Histology shows keratinocyte edema causing ballooning degeneration and acantholysis, intranuclear inclusion bodies, and dense inflammatory infiltrate  $\pm$  epidermal/adnexal necrosis
- **Treatment:** acyclovir, valacyclovir, famciclovir; if acyclovir-resistant use foscarnet or cidofovir



**Figure 4.2**

**A: Eczema herpeticum**

(Courtesy of Dr. Sophie M. Worobec)

**B: Perianal HSV ulcers**

(Reprint Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. 2nd ed. St. Louis, MO: Mosby Elsevier; 2008)

**C: HSV corneal ulcer**

(Reprint from Mandell G, ed. *Atlas of Infectious Diseases*. Philadelphia, PA: Current Medicine LLC; 2002)



**Varicella-Zoster-Virus (HHV3, VZV, Herpes Zoster) (Figure 4.3B, C)**

- Initial infection causes varicella (Figure 4.3A) and following resolution, virus lies dormant in spinal dorsal root ganglion until reactivation as herpes zoster
- Of note, women with varicella infection 5 days before or 2 days after delivery can result in severe acute infection of newborn (neonatal varicella, mortality of newborn up to 30%); different from VZV embryopathy or congenital varicella syndrome which occurs in first 20 weeks of pregnancy
- Zoster: 75% cases with precedent prodromal pain/paresthesias, followed by grouped, painful erythematous macules/papules along single sensory dermatome (rarely crossing midline) → vesicles/bullae → rupture forming hemorrhagic crust and become dry over 7–10 days; lesions are infectious until dry
- Atypical presentation in AIDS pts: >2 dermatomes affected, may cross midline, may present with verrucous or crusted lesions
- Complications: postherpetic neuralgia (PHN), scarring, secondary bacterial infection, meningoencephalitis, Ramsay–Hunt syndrome, ocular blindness, motor paralysis
- Ocular involvement: lesions on tip of nose signal possible ocular infection (since nasociliary nerve involved, which is a branch of the ophthalmic nerve)
- **Ramsay–Hunt syndrome:** infection of geniculate ganglion → ear canal/auricle/tympanic membrane involvement with painful vesicles, facial paralysis/paresis, ipsilateral hearing loss
- Visceral involvement (hepatitis, pneumonitis, encephalitis, etc) may occur with disseminated zoster in immunocompromised patients
- Treatment: antiviral best if within 48–72 h within appearance of rash (can ↓ PHN risk); of note, concomitant corticosteroid use has no effect on development/duration of PHN; IV acyclovir used in immunocompromised patient if advanced HIV, widespread skin involvement, visceral disease or transplant patients

**Figure 4.3**

**A:** Disseminated varicella  
 (Courtesy of Dr. Sophie M. Worobec)  
**B:** Herpes zoster, trunk  
**C:** Herpes zoster, magnified



### Epstein–Barr Virus (EBV, HHV4)

- Infects B lymphocytes and establishes lifelong asymptomatic infection in these cells and mucosal epithelial cells
- Causes infectious mononucleosis (IM), oral hairy leukoplakia (OHL), Gianotti–Crosti syndrome, Hodgkin’s lymphoma, endemic Burkitt’s lymphoma, posttransplant lymphoproliferative disorder (PTLD), nasopharyngeal carcinoma, and NK cell lymphoma
- Of note, morbilliform eruption typically occurs in patients with mononucleosis if ampicillin or amoxicillin given

### Cytomegalovirus (CMV, HHV5)

- Asymptomatic/subclinical infection in healthy persons, but severe infections in infants infected before birth and immunosuppressed patients (especially with HIV or organ transplantation); transmission via body fluids
- Immunosuppressed patient: infection can lead to ocular involvement (CMV necrotizing retinitis), CNS involvement (meningoencephalitis), GI tract involvement (inflammation with painful ulcerations), and lung abnormalities (pneumonitis)
- Presents with wide variation: asymptomatic or mono-like symptoms; polymorphous eruption including vesicles, nodules, or verrucous plaques
- Histology: cytomegalic endothelial and/or epithelial cells enlarged with intranuclear inclusions, eccentrically displaced nucleus with halo (“owl’s eye” inclusion bodies)
- In patients with HIV can present with chronic perianal and lower extremity ulcerations, esophagitis, pneumonitis, chorioretinitis
- Treatment of choice is ganciclovir

### HHV6

- Etiologic agent of exanthem subitum (roseola infantum or sixth disease)
- Transmission via saliva with lifelong latency after primary infection
- Complications infrequent in healthy patients: most common include febrile seizures
- Treatment: no treatment required in healthy patients

### HHV7

- Epidemiology similar to HHV6
- Not clearly associated with any clinical disease, but it has been linked to several conditions such as exanthem subitum and pityriasis rosea (Figure 4.4A–C, 4.5A)



**Figure 4.4**  
**A:** Pityriasis rosea, herald patch  
**B:** Pityriasis rosea  
**C:** Pityriasis rosea  
 (Courtesy of Dr. Paul Getz)

**HHV8 (Kaposi Sarcoma-Associated Herpesvirus [KSHV])**

(Figure 4.5B)

- Etiologic agent of all types of Kaposi's sarcoma (KS)
- Four types of KS:
  - **Classic:** indolent, purple-red plaques on lower extremities in elderly men from Mediterranean descent, slow progression, rare involvement of GI tract and oral mucosa
  - **AIDS-related:** widely distributed purpuric macules, patches and plaques on skin, oral and genital mucosa, GI tract, and lung
  - **Immunosuppression-associated:** similar to AIDS-related KS with aggressive nature and dissemination
  - **African endemic:** aggressive, young patients in equatorial Africa, unrelated to HIV, subtypes include nodular, lymphadenopathic, florid, and infiltrative
- Other conditions associated with HHV8: Castleman's disease (nonmalignant lymphoproliferative disorder) and primary effusion lymphoma
- Histology: spindle cells forming slit-like vascular channels with surrounding hemosiderin, promontory sign
- Treatment: topical retinoid, surgery, radiotherapy, cryotherapy, systemic chemotherapy for extensive disease, HAART if AIDS-related

**B. HUMAN PAPILLOMAVIRUS (HPV)**

- Non-enveloped dsDNA virus with more than 100 different HPV types; infects epithelia and mucosa
- Genome encodes "E" (early) and "L" (late) proteins
  - **"E" proteins** (E1–E7) code for viral DNA replication; E6 and E7 oncogenes lead to keratinocyte immortalization; low levels expressed in basal layer
  - **"L" proteins** (L1 and L2) code for viral structural proteins (form outer shell: virion), expressed in superficial epithelium
- Transmission mainly via direct skin contact, less likely via fomites; basal keratinocyte target of HPV (long-term reservoir of viral DNA)
- Divided into nongenital and genital infections; also divided into benign or low risk (HPV 6/11) and high risk (HPV 16/18) types
- Gardasil® vaccine: composed of L1 capsid protein with four types of recombinant HPV (type 6, 11, 16, 18)
- Cervarix® vaccine: L1 protein for HPV 16 and 18
- Clinical manifestations of HPV infection:
  - **Common, plantar, and flat warts** (Figure 4.5C)
  - **Condyloma acuminata:** lesions without significant scale in genital area

**Figure 4.5****A: Pityriasis rosea, face**

(Courtesy of Dr. Paul Getz)

**B: Kaposi's sarcoma**

(Courtesy of National Cancer Institute)

**C: Verruca vulgaris**

- **Bowenoid papulosis:** red-brown papules or plaques involving genital and/or perineal area (clinically appear as genital warts, but histology consistent with Bowen's disease) (Figure 4.6A)
- **Verrucous carcinoma:** "semi-malignant" (Figure 4.6B)
  - Florid oral papillomatosis: widespread verrucous carcinoma in oral cavity
  - Buschke–Lowenstein tumor: large cauliflower-like tumor of anorectum and external genital, focal malignant transformation may occur
  - Epithelioma cuniculatum of sole: slow-growing warty mass on sole
- **Focal epithelial hyperplasia** (Heck's disease): papules on buccal, gingival, labial mucosa resembling flat warts
- **Epidermodysplasia verruciformis:** sporadic or AR inheritance, abnormal susceptibility of skin to HPV; red-brown macules with mild scale on face/trunk or flat-topped papules on hands resembling flat warts (malignant transformation in 50% patients)
- Histology: papillomatosis, massive orthokeratosis, columns of parakeratosis, coarse keratohyalin granules of variable size, vacuolated cells (koilocytes), dilated and thrombosed capillaries



Table 4-1 HPV Subtypes

Lesion	HPV Types (Frequent)	HPV Types (Less Frequent)
Common wart	1, 2, 4	26, 27, 29, 41, 57, 60, 63, 65
Plantar wart	1	2, 4, 63
Flat wart	3, 10	28, 29
Butcher's wart	2, 7	1, 2, 3, 4, 10, 28
Epidermodysplasia verruciformis (EV)	2, 3, 5, 8–10, 12, 14, 15, 17	19–25, 36–38, 46, 47, 49, 50
Focal epithelial hyperplasia (Heck's)	13, 32	Different sources will have conflicting HPV types for same entity
Verrucous carcinoma	6, 11	
Condyloma acuminata	6, 11	40, 42–44, 51, 54, 55, 61, 70, 72, 81
Bowenoid papulosis	16, 18	26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 62, 66, 68, 73
Digital SCC	16	34, 35
SCC (in EV)	5, 8	14, 17, 20, 47
Cervical cancer	16, 18	31, 33, 35, 39, 45, 51, 52, 56, 58, 66, 68, 70

**Figure 4.6****A: Bowenoid papulosis\*****B: Verrucous carcinoma on lip in betel leaf chewer\***

\*Courtesy of Dr. Shyam B. Verma, Vadodara, India

## C. POXVIRUS INFECTIONS

**Table 4-2 Select Poxvirus Infections**

Disease	Virus	Clinical Findings	Treatment	Comments
<b>Molluscum contagiosum</b>	Molluscipox ↓ Molluscum contagiosum virus	Umbilicated pink, firm waxy papules seen mainly in children  If adult with genital lesions, likely sexual transmission  Larger lesions seen in patients with AIDS	Usually self-limited  Treatment: catharidin, cryosurgery, curettage, imiquimod	<b>Henderson-Patterson molluscum bodies on histology</b> (intracytoplasmic inclusion bodies)
<b>Orf</b> (Contagious pustular dermatosis) (Ecthyma contagiosum)	Parapox ↓ Orf virus	One to few papules at contact site with infected goat/sheep, ± fever, lymphadenitis; six clinical stages (in order; maculopapular, targetoid, acute, regenerative, papillomatous, regressive)	Supportive treatment as self-limited	Mainly in <b>shepherds, veterinarians, goat herders, and butchers</b>
<b>Milker's nodule</b> (Pseudocowpox) (Paravaccinia)	Parapox ↓ Paravaccinia virus	Presents as solitary red-purple nodule on finger with slow growth or with multiple cherry-red nodules at inoculation site	Supportive treatment as self-limited	Recent contact with <b>infected cows, calves</b> , or viral fomites
<b>Vaccinia</b>	Orthopox ↓ Vaccinia virus	Local reaction to site of vaccination (erythema or pruritic papule)  <b>Eczema vaccinatum</b> (in atopic patients): diffuse infection in eczematous skin	Supportive; heals with pitted scarring	<b>Live virus used for smallpox vaccine</b>
<b>Smallpox</b>	Orthopox ↓ Variola virus	Prodrome (backache, fever) after incubation period  Macules/papules initially on face, spreads to trunk and extremities → papules turn to vesicles/pustules with central umbilication	Respiratory and contact isolation, vaccination if early	All lesions <b>same stage of development</b>  Transmission via respiratory droplets
<b>Cowpox</b>	Orthopox ↓ Cowpox virus	Painful inflamed macule or papule at contact site with infected cow → vesicular, then pustular with tendency to ulcerate → deep-seated black eschar with erythema	Supportive as self-limited; heals with scarring	Eschar with surrounding edema/erythema <b>similar to cutaneous anthrax</b>



## D. MISCELLANEOUS

**Table 4-3 Classification of Viruses**

RNA	dsDNA	ssDNA
Togavirus (rubella)	Herpesvirus (HSV, CMV, EBV, KSHV)	Parvovirus
Flavivirus (HCV, dengue fever, yellow fever)	Hepadnavirus (HBV)	
Orthomyxovirus (influenza)	Adenovirus	
Rhabdovirus (rabies)	Papovavirus (papillomavirus, JC virus)	
Picornavirus (rhinovirus, hepatovirus [HAV], enterovirus [poliovirus, enterovirus, coxsackievirus, echovirus])	Poxvirus (molluscipox, orthopox, parapox)	
Paramyxovirus (measles, mumps, RSV)	DNA virus mnemonic: <b>HHAPPPy</b>	
Retrovirus (HIV, HTLV)		

**Table 4-4 Select Vaccinations**

Live Attenuated Virus	Killed Virus	Purified Products
Influenza ( <b>nasal spray</b> , FluMist®)	Influenza ( <b>injection</b> )	Pneumococcus (Pneumovax®)
Yellow fever	Rabies	Tetanus
Typhoid (oral)	Typhoid (injection)	Hepatitis B
Polio ( <b>oral</b> )	Polio ( <b>injection</b> )	Diphtheria
Rubella	Hepatitis A	HPV (Gardasil®)
Mumps	Cholera	HPV (Cervarix®)
Measles	Bubonic plaque	
BCG ( <i>M. bovis</i> )		
VZV (Zostavax®)		

**LIVE VIRUS: ROME Is MY Best Vacation:** rubella, oral polio, mumps, influenza, measles, yellow fever, bcg, varicella

**KILLED/PURIFIED VIRUS:**  
Rest in **PPPeace** Always: rabies, influenza, polio (injection), pneumococcus, papillomavirus, **A** hepatitis (and B)

## 4.2 BACTERIAL INFECTIONS

### A. GRAM-POSITIVE INFECTIONS

#### STAPHYLOCOCCAL INFECTIONS

- *S. aureus*: aerobic, gram-positive catalase-positive bacteria arranged in clusters
- Best defense: intact skin
- MRSA: ↑ resistance to methicillin caused by staphylococcal chromosome cassette mec (SCC mec), specifically mecA gene (encodes alternative penicillin-binding protein, PBP2a)
- Select *S. aureus* toxins:

<b>Toxic shock syndrome toxin-1 (TSST-1)</b>	Superantigen, involved in toxic shock syndrome (TSS)
<b>Exfoliative toxin (ET-A, ET-B)</b>	Protease activity, splits epidermal desmoglein 1, involved in staphylococcal scalded skin syndrome (SSSS) and bullous impetigo
<b>Panton–Valentine leukocidin (PVL)</b>	In many community-acquired <u>MRSA strains</u> , associated with ↑ virulence (leukocyte destruction, necrosis)

#### Impetigo (Figure 4.7A, B)

- Highly contagious infection seen primarily in children
- Two types: bullous and nonbullous
- Nonbullous: *S. aureus* most common cause, less common Gr. A strep (GAS)
  - Erythematous macule → pustule/vesicle → erosion with golden crust (+ culture from exudate under crust)
- Bullous: *S. aureus* ONLY (usually phage II, type 71)
  - Flaccid, transparent bullae → rupture leaving shiny, dry erosion with no surrounding erythema, ± fever, diarrhea, weakness
  - Cleavage at granular layer due to ET (A/B) binding to desmoglein 1; *S. aureus* at site of lesion ← Unlike SSSS
- Treat with topical mupirocin, if extensive can use oral antibiotic (i.e., cephalexin, dicloxacillin, etc.)

#### Staphylococcal Scalded Skin Syndrome (SSSS) (Figure 4.7C)

- Exfoliative disease mainly in neonates and young children; can occur in adults with renal insufficiency or if immunocompromised (mortality > 50%)
- Presents with fever, conjunctivitis, initial tenderness of skin and erythema over body folds → generalized wrinkled appearance with subsequent exfoliation (“sad man” facies), perioral crusting/fissuring, + Nikolsky sign
- *S. aureus* phage II (types 3A, 3C, 55, or 71) present at a distant site (extralesional): ET (A/B) - binds desmoglein 1 in granular layer causing superficial bulla
- Culture of bullae - negative (infection at remote site)
- Treatment: penicillinase-resistant penicillin (i.e., dicloxacillin) and IV fluid support



**Figure 4.7**

**A: Impetigo**

(Courtesy of Dr. Paul Getz)

**B: Bullous impetigo, arm**

**C: SSSS**

(Reprint from Allen HB. *Dermatology Terminology*. New York, NY: Springer; 2010)

**Toxic Shock Syndrome (TSS)** (Figure 4.8A)

- Multisystem illness due to *S. aureus*, initially in women with use of superabsorbent tampons, but now more commonly seen in infections with wounds, catheters, deep abscesses, or nasal packing
- Superantigen-mediated TSST-1 results in polyclonal T-cell activation → cytokine storm (TNF, IL-1, etc)
- Presentation:
  - Four criteria: fever, hypotension, macular exanthem, and involvement of three or more organ systems
  - Exanthem: diffuse scarlatiniform exanthem on trunk spreading outward, palmoplantar edema, and erythema (with desquamation 1–3 weeks later), hyperemia of conjunctiva
- Treatment: remove any nidus of infection, parenteral  $\beta$ -lactamase resistant antibiotic, and fluid support

**Bacterial Folliculitis**

- Superficial infection of hair follicle usually due to *S. aureus*
- Presents with pustules in follicular distribution associated with hairs
- Treatment: antibacterial wash (chlorhexidine or triclosan), antibacterial ointments (mupirocin), and if widespread can use oral antibiotic

**Furuncle, Carbuncle, Abscess** (Figures 4.8B, C, 4.9A)

- Typically due to *S. aureus*
- Depth of infection determines presentation
- **Furuncle**: deep-seated tender nodule of hair follicle
- **Carbuncle**: coalescing of adjacent furuncles with multiple draining sinuses (typically involves nape of neck or back of thighs)
- **Abscess**: inflamed walled-off collection of pus
  - Treatment
    - Simple furuncle (no fluctuance): warm compresses
    - Fluctuant furuncle or abscess: incision and drainage
    - Oral antibiotics if:
      - Located near midface (due to concern for cavernous sinus thrombosis) or external auditory canal
      - Recurrent or recalcitrant
      - Very large or with surrounding cellulitis

**Figure 4.8****A: Toxic shock syndrome**(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)**B: Carbuncle****C: Abscess**



**STREPTOCOCCAL INFECTIONS**

- Gram-positive bacteria arranged in chains or pairs
- Not part of normal cutaneous flora (but resident of aerodigestive tract and vagina)
- Classification via two methods:
  - Ability to induce hemolysis ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) and/or
  - Lancefield groups (A–D, G) based on characteristic polysaccharide cell wall
  - Of note, group A  $\beta$ -hemolytic streptococci (*S. pyogenes*, GAS) most pathogenic
- The following antibodies become positive after infection with GAS: antistreptolysin O (ASO), antihyaluronidase, and anti-DNase-B
- Certain strains with erythrogenic toxins: *S. pyogenes* exotoxins (SPE-A, SPE-B, SPE-C)

**Cellulitis (Figure 4.9B)**

- Infection of the deep dermis and subcutaneous tissue, mostly due to GAS (*S. aureus* less common)
- In immunocompetent patients, usually the first step is a break in the skin barrier
- Presents as an ill-defined area with erythema, swelling, and tenderness,  $\pm$  fever, chills
- Treatment: oral antibiotic with good Gram-positive coverage

**Erysipelas (St. Anthony's Fire) (Figure 4.9C)**

- Superficial type of cellulitis with significant dermal lymphatic involvement; typically due to GAS
- Presents as a well-defined, bright red indurated plaque with sharp, raised borders commonly on the face or legs,  $\pm$  constitutional symptoms
- Treatment of choice: PCN (if PCN-allergic can use macrolide)

**Blistering Distal Dactylitis**

- Unique GAS bullous eruption in children
- Tense stable blisters on tender erythematous base over volar tips of toes or fingers
- Treatment: dicloxacillin or first-generation cephalosporin

**Necrotizing Fasciitis**

- Rapidly progressive necrosis of subcutaneous tissue and fascia due to GAS, but typically mixed infection with 30% mortality rate
- Risk factors include advanced age, diabetes, peripheral vascular disease, and/or history of alcohol abuse
- Presents as tender, erythematous tense plaques recalcitrant to antibiotics and progresses at an alarming rate  $\rightarrow$  necrosis of fascia and fat renders watery foul-smelling fluid
- Treatment: extensive surgical debridement

**Figure 4.9****A: Abscess**

(Courtesy of Dr. Paul Getz)

**B: Cellulitis**

(Courtesy of Dr. Paul Getz)

**C: Erysipelas**

(Courtesy of CDC: Dr. Thomas Sellers, Emory University)



**Perianal Streptococcal Disease (Figure 4.10A)**

- Perianal GAS infection typically in preschool children
- Presents with a circular band of erythema around anus,  $\pm$  painful defecation, blood-streaked stools, anal leakage
- Obtain both throat and perianal culture; treat with PCN or erythromycin  $\times$  10–14 days

**Ecthyma (Figure 4.10B)**

Do not confuse with ecthyma gangrenosum

- Deeper form of nonbullous impetigo with ulceration due to GAS but quickly contaminated by *S. aureus*
- Presents as “punched out” shallow ulcer with thick, yellow-gray crust commonly in lower legs of children
- If diagnosis uncertain  $\rightarrow$  punch biopsy with deep-tissue Gram stain and culture
- Treatment: dicloxacillin or first-generation cephalosporin

**Scarlet Fever (Figure 4.10C)**

- Diffuse exanthem from GAS pharyngitis with erythrogenic toxin (SPE-A, B, C); mainly in children
- Presents with sore throat, headache, fever  $\rightarrow$  tiny pink papules on erythematous background (sandpaper-like), linear petechiae streaks along body folds (Pastia’s lines), circumoral pallor, palatal petechiae, “strawberry tongue”
- Treatment: PCN or erythromycin  $\times$  10–14 days

**Streptococcal Toxic Shock Syndrome (STSS)**

- Rapidly progressive multiorgan illness, high mortality (30–60%), caused by GAS
- Superantigen mediated: SPE-A  $\rightarrow$  stimulates T cells with massive cytokine release  $\rightarrow$  subsequent shock
- Presents typically with sudden onset pain in an infected soft tissue, flu-like symptoms, CNS symptoms (confusion, coma)  $\rightarrow$  multiorgan failure
- Generalized exanthem less common in STSS (vs. TSS), and STSS more likely in an otherwise healthy adult
- Treatment: intensive supportive therapy, IV penicillinase-resistant PCN or oral clindamycin (latter may more rapidly shut down toxin production)

**Figure 4.10****A: Perianal strep**

(Reprint from Al-Jasser M, Al-Khenaizan S. Cutaneous mimickers of child abuse. *Eur J Ped.* 2008; 167(11): 1221–30)

**B: Ecthyma**

(Courtesy of Dr. Paul Getz)

**C: Strawberry tongue**

(Reprint from Allen HB. *Dermatology Terminology*. New York, NY: Springer; 2010)

## CORYNEBACTERIAL INFECTIONS

- *Corynebacterium*: gram-positive rod-shaped bacteria

### Erythrasma (Figure 4.11A, B)

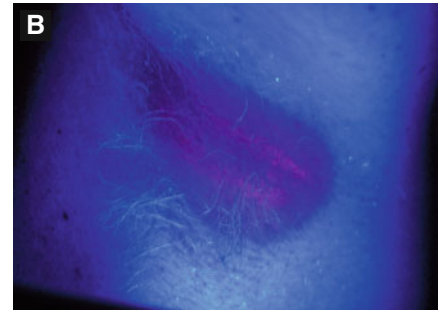
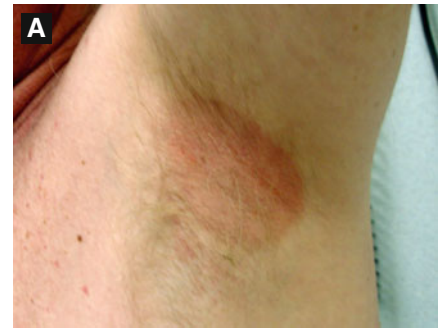
- Superficial infection in occluded intertriginous areas due to *C. minutissimum*
- Presents as well-demarcated red-brown macules/patches with fine scale and wrinkling in intertriginous areas; interdigital maceration and scaling between toes
- Most common bacterial infection of the foot
- Wood's lamp: bright coral-red fluorescence due to porphyrin production (coproporphyrin III)
- Treatment: topical antibiotic or antifungal (clindamycin, erythromycin, imidazole) or oral erythromycin × 5 days

### Trichomycosis Axillaris

- Superficial bacterial colonization with *C. tenuis* of hair shafts in axilla; ↑ risk with hyperhidrosis/poor hygiene
- Presents with white-yellow, red, or black adherent nodules attached to hair shafts ("frosted" appearance of hairs) with characteristic rancid acidic odor, common in axilla, and rarely affects pubic area
- Treatment: shave axillary hair, topical benzoyl peroxide or topical clindamycin

### Pitted Keratolysis (Figure 4.11C, D)

- Noninflammatory infection due to *Corynebacteria* spp. or *Kytococcus sedentarius* (previously called *Micrococcus*)
- Bacteria produce keratin-degrading proteases
- Presents with asymptomatic shallow crater-like depressions over weight-bearing areas of feet, accompanying hyperhidrosis and malodor
- Treatment: topical clindamycin, erythromycin, or benzoyl peroxide



**Figure 4.11**

**A:** Erythrasma

**B:** Erythrasma (Wood's light)

**C:** Pitted keratolysis

(Courtesy of Dr. Paul Getz)

**D:** Pitted keratolysis

(Courtesy of Dr. Paul Getz)

**Cutaneous Diphtheria** (Figure 4.12A)

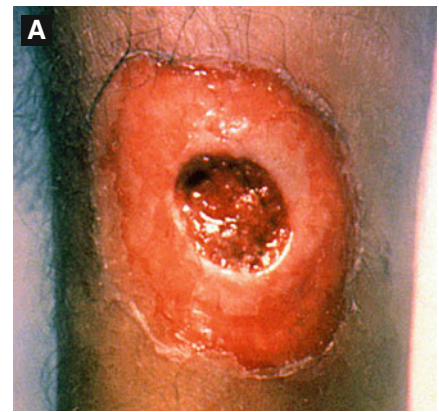
- Localized infection of *C. diphtheriae*, endemic in several tropical countries, skin involvement via inoculation to an otherwise insignificant wound
- Presents as sharply bordered, punched out ulcer with yellow leathery pseudomembrane (primary disease) or preexisting wound becomes infected (secondary disease)
- If toxin produced, risk of cardiac or neurologic disease
- Treatment: diphtheria antitoxin from horse serum (before toxin binds cells) crucial, PCN or erythromycin  $\times 10\text{--}14$  days

**OTHER GRAM-POSITIVE INFECTIONS****Anthrax (Malignant Pustule)** (Figure 4.12B)

- Acute disease in humans and animals caused by *Bacillus anthracis*, a Gram-positive spore-forming rod
- Clinical forms: cutaneous, pulmonary, and GI
- **Cutaneous form:** “malignant pustule” at inoculation site which spreads and becomes hemorrhagic  $\rightarrow$  central eschar with surrounding nonpitting edema  $\rightarrow$  eschar sloughs leaving shallow ulceration
- Virulence factors: capsule and two exotoxins: edema toxin (increases cAMP levels) and lethal toxin (increases TNF $\alpha$  and IL1 $\beta$  promoting shock/death)
- Bioterrorism-associated treatment: ciprofloxacin or doxycycline (conventional treatment: PCN)

**Erysipeloid (Fish Handler’s Disease)** (Figure 4.12C)

- Infection caused by *Erysipelothrix rhusiopathiae* through direct contact with infected meat, seen mainly in meat-handlers, fisherman, or veterinarians
- Presents with painful red to purple patches over hands (finger webs often involved, sparing terminal phalanges) with sharply margined spreading edge, possible central clearing, and/or hemorrhagic vesicles
- Systemic form with fever, arthralgias, widespread cutaneous lesions, possible sepsis, and fatal endocarditis
- Treatment: penicillin (if PCN allergy  $\rightarrow$  erythromycin)

**Figure 4.12****A: Cutaneous diphtheria**

(Courtesy of Public Health Image Library: CDC)

**B: Cutaneous anthrax**

(Courtesy of James Steele, CDC)

**C: Erysipeloid**

(Reprint from Mandell G, ed. Atlas of Infectious Diseases. Philadelphia PA: Current Medicine LLC; 2002)



**Actinomycosis ("Lumpy Jaw")** (Figure 4.13A, B)

- Due to *Actinomyces israelii*, an anaerobic filamentous Gram-positive bacteria; part of normal oral flora
- Risk factors: poor dental hygiene, dental procedures, traumatic injuries
- Presents as a firm nodule or bluish swelling at angle of jaw → direct spread into adjacent tissues → formation of fistulas discharging purulent material with granules (yellow sulfur-like appearance consisting of masses of bacteria, both gram-negative and gram-positive)
- Treatment: intravenous PCN initially, then switch to oral PCN × 6–12 months

**Actinomycetoma (Madura Foot)** (Figure 4.13C)

- Suppurative infection caused by bacteria (actinomycetoma) or fungus (eumycetoma)
- Bacterial infection due to *Nocardia brasiliensis*, *Nocardia asteroides*, *Actinomadura madurae*, *Actinomadura pelletieri*, *Streptomyces somaliensis*
- Presents as painless nodules at site of trauma (typically on foot) → increases in size with purulence, tumefaction, draining sinuses, and exudate containing grains
- Treatment: surgical debridement, trimethoprim-sulfamethoxazole (if sulfa-allergic, can use minocycline)



Grain Color	Organism
White	<i>Nocardia brasiliensis</i> , <i>Nocardia asteroides</i>
Pink or cream	<i>Actinomadura madurae</i>
Yellow to brown	<i>Streptomyces somaliensis</i>
Red	<i>Actinomadura pelletieri</i>

**B. GRAM-NEGATIVE INFECTIONS****PSEUDOMONAL INFECTIONS**

- *Pseudomonas aeruginosa*: gram-negative bacteria, grows well in aqueous environment, has ability to produce variety of pigments:
  - Greenish-blue pyocyanin
  - Yellow-green fluorescein
  - Brown-black pyomelanin

**Green Nail Syndrome** (Figure 4.13D)

- Subungual pseudomonal infection causing green discoloration of nail and onycholysis
- Treatment: trim nail, acetic acid soaks, topical ciprofloxacin, or thymol solution

**Figure 4.13****A: Actinomycosis**

(Courtesy of Dr. Paul Getz)

**B: Actinomycosis, chest**

(Courtesy of Dr. Vandana Mehta, India)

**C: Actinomycetoma, arm**

(Courtesy of Dr. Paul Getz)

**D: Green nail syndrome**



### Ecthyma Gangrenosum (Figure 4.14A)

- Cutaneous manifestation of severe, invasive infection by *P. aeruginosa* typically in immunosuppressed patients
- Presents initially as erythematous macules → opalescent, tense vesicles or pustules → hemorrhagic and violaceous vesicles → rupture and form ulcers with necrotic centers
- Treatment: intravenous aminoglycoside with anti-pseudomonal penicillin

### Pseudomonas Hot Foot Syndrome

- Painful plantar purple-red nodules after exposure to pool water contaminated with *P. aeruginosa*
- Self-limited

### Pseudomonal Folliculitis (Hot Tub Folliculitis)

- Folliculitis due to nonpathogenic strain of *P. aeruginosa*
- Presents with erythematous follicular papules and pustules at sites of exposure to water (via whirlpool, hot tub, rarely swimming pool) with sparing of face and neck
- Self-limited in immunocompetent person

### Pseudomonal Pyoderma

- Superficial infection of skin with *P. aeruginosa* with “mousy” odor
- Presents typically on feet with macerated “moth-eaten” appearance, green-blue purulence, and eroded borders
- Blastomycosis-like pyoderma presents as verrucous plaques with elevated borders and pustules as a chronic vegetating infection

## OTHER GRAM-NEGATIVE INFECTIONS (Table 4-5)

### Acute Meningococcemia (Figure 4.14B, C)

- Acute and potentially life-threatening infection of the blood vessels caused by *Neisseria meningitidis*, an encapsulated gram-negative diplococcus
- Bacterial carriage via nasopharynx
- Presents initially with erythematous macules/papules → evolve to stellate purpuric patches/plaques with ischemic necrosis and/or hemorrhage, accompanied by high fever and toxic appearance
- Recurrent infections in patients with defects in late components of complement (C5–C9)
- Treatment: high dose IV PCN (if resistant, use third-generation cephalosporin)



**Figure 4.14**

**A: Ecthyma gangrenosum**

**B: Meningococcemia**

(Courtesy of Dr. Paul Getz)

**C: Meningococcemia**

(Courtesy of Dr. Paul Getz)

**Table 4-5 Select Gram-Negative Infections**

Disease	Etiology/Vector	Clinical Findings	Treatment
<b>Glanders</b>	<i>Burkholderia mallei</i> Contact with infected horses	Ulcerated nodule at inoculation site with regional lymphadenopathy, ± “farcy buds” (nodules along lymph nodes)	Sulfonamide
<b>Brucellosis</b> (Undulant fever) (Malta fever)	<i>Brucella</i> spp. Direct contact with infected animal or ingestion of dairy (unpasteurized) infected meat	Cyclic fevers, arthralgias, hepatosplenomegaly; rare skin involvement (violaceous papulonodular eruption) ↑ Risk: butchers, farmers, veterinarians	Doxycycline combined with rifampin
<b>Tularemia</b> (Rabbit fever) (Deer fly fever)	<i>Francisella tularensis</i> Direct contact with wild animals like <u>rabbits</u> (rabbit-borne), ticks (tick-borne) or deer flies	Ulceroglandular: tender chancre-like papule or nodule with lymphadenopathy, lymph nodes may become fluctuant with suppuration ↑ Risk in <b>hunters</b>	Streptomycin
<b>Vibrio infection</b>	<i>Vibrio vulnificus</i> Ingestion of raw seafood or open wound exposed to seawater	Fever, chills, abdominal pain, red to violaceous macules → painful hemorrhagic bullae with cellulitis ↑ Risk: diabetes, liver disease, immunosuppression	Oral TCN
<b>Plague</b>	<i>Yersinia pestis</i> Transmitted via flea bite from infected animals	Myalgias, malaise, fever → small papule/pustule at site of flea bite with swollen, painful fluctuant lymph nodes (“buboes”)	Streptomycin (IM)
<b>Malakoplakia</b>	<i>E. coli</i> (± <i>Pseudomonas aeruginosa</i> , <i>Proteus</i> , <i>Klebsiella</i> )	Commonly affects urinary tract, rare skin involvement with weeping perianal plaque or polypoid mass Histo: <b>Michaelis–Gutmann bodies</b>	Cipro (long-term) or surgical removal
<b>Rhinoscleroma</b>	<i>Klebsiella rhinoscleromatis</i> Transmission via inhalation of droplets or contaminated material	Infectious granulomas in nasal mucosa and respiratory tract, epistaxis, Hebra nose (destruction of nasal cartilage) Histo: <b>Mikulicz cell, Russell bodies</b>	Cipro
<b>Rat-Bite Fever</b> (Haverhill fever)	<i>Streptobacillus moniliformis</i> Direct contact from rodents or contaminated food	Fever, arthritis, ± ulceration at site of bite and generalized morbilliform eruption with acral distribution	Pencillin
<b>Cat Bite</b>	<i>Pasteurella multocida</i>	Erythema, pain, tenderness with gray serous drainage from puncture wound	Augmentin, irrigate site, ± tetanus prophylaxis
<b>Dog Bite</b>	<i>Capnocytophaga canimorsus</i> <i>Pasteurella canis</i> <i>Pasteurella multocida</i>		
<b>Human Bite</b>	<i>Eikenella corrodens</i>		

**BARTONELLA INFECTIONS**

- Gram-negative, facultative intracellular bacteria
- Can infect healthy individuals but considered especially important as an opportunistic pathogen
- Transmitted via insect vectors (ticks, fleas, sand flies, and mosquitoes)
- Adheres to and invades erythrocytes (*B. bacilliformis*)
- All three types can produce an endothelial cell-stimulating factor → causes proliferation of both endothelial cells and blood vessels

**Table 4-6 Select Bartonella Infections**

Disease	Etiology/Vector	Clinical Findings	Treatment
<b>Oroya Fever</b> (Carrion's disease) (Verruga peruana) (Peruvian wart)	<i>Bartonella bacilliformis</i> Vector: sandfly <i>Lutzomyia verrucarum</i>	Biphasic disease - <u>Acute stage</u> (Oroya fever): fever + hemolytic anemia - <u>Chronic stage</u> (verruca peruana): erythematous papules/nodules, resolves spontaneously but may persist for years	Acute stage: <u>chloramphenicol</u> (covers salmonella coinfection) Chronic stage: TCN or PCN
<b>Cat-Scratch Disease</b>	<i>Bartonella henselae</i> Vector: cat flea <i>Ctenocephalides felis</i>  Transmission via cat bite or scratch (flea feces inoculated into scratch site)	Unilateral tender lymphadenitis 2–4 weeks after cat scratch, typically in axilla > epitrochlear node (can last between 2 and 5 months)  <u>Parinaud oculoglandular syndrome</u> : unilateral conjunctivitis and regional lymphadenitis	Spontaneous resolution typical  If patient immunosuppressed, treat with doxycycline or erythromycin
<b>Bacillary Angiomatosis</b>	<i>Bartonella henselae</i> , <i>Bartonella quintana</i> Vector: lice, ticks, fleas	Erythematous tender papules and nodules resembling pyogenic granulomas, seen mainly in HIV patients	Doxycycline or erythromycin
<b>Trench Fever</b> (Shinbone fever)	<i>Bartonella quintana</i> Vector: body louse  <i>Pediculus humanus var. corporis</i>	Fever (relapsing), chills, tenderness of shins, back pain, and transient macular eruption  ↑ Risk: crowding and poor hygiene	Doxycycline or erythromycin

Also causes epidemic typhus

**RICKETTSIAE**

- Gram-negative, motile, pleomorphic bacteria; obligate intracellular parasite (usually infecting endothelial cells, causing vasculitis)
- Bacteria carried as parasites by many ticks, fleas, and lice
- Includes *R. rickettsii*, *R. akari*, *R. conori*, *R. prowazekii*, *R. typhi*, *R. tsutsugamushi* (latter reclassified into genus *Orientia*)
- Few bacteria which are morphologically similar to *Rickettsiae*: *Coxiella burnetii* and *Ehrlichia*

**Table 4-7 Select Rickettsial Infections**

Disease	Organism/Vector	Clinical Findings	Treatment
<b>Rocky Mountain Spotted Fever (RMSF)</b>	<i>R. rickettsii</i> Vector: tick <i>Dermacentor andersoni</i> (wood tick in Western US) <i>Dermacentor variabilis</i> (dog tick in Eastern US)	Fever, headache, myalgias → purpuric or hemorrhagic macules and papules on wrists/ankles initially → spreads to trunk, hands, feet ("spotless" in 10–20% cases) Mortality 15–25% if untreated	Doxycycline preferred treatment (in pregnant patients may use chloramphenicol)
<b>Mediterranean Spotted Fever (Boutonneuse fever)</b>	<i>R. conorii</i> Vector: brown dog tick <i>Rhipicephalus sanguineus</i>	Two forms - <b>Tache noir</b> : indurated papule at site of tick bite → necrotic ulcer - <b>Exanthem</b> : erythematous papules mainly over lower limbs	Doxycycline or chloramphenicol
<b>Rickettsialpox</b>	<i>R. akari</i> Vector: mouse mite <i>Liponyssoides sanguineus</i> (formerly <i>Allodermanyssus</i> )	Initial papule or vesicle at site of bite → Eschar, regional lymphadenopathy → Sudden-onset fever, chills, headache, diffuse vesicular rash (self-limited)	Doxycycline or chloramphenicol
<b>Epidemic Typhus (Louse-borne)</b>	<i>R. prowazekii</i> Vector: body louse <i>Pediculus humanus var. corporis</i> Reservoir: flying squirrel	Fever, chills, headache → pale red macules on trunk → evolve to petechiae papules, spread to rest of body (spare face, palms, and soles) Vascular inflammation of skin, CNS, heart, kidneys, and muscle	Doxycycline or chloramphenicol
<b>Endemic Typhus (Flea-borne) (Murine typhus)</b>	<i>R. typhi</i> Vector: rat flea <i>Xenopsylla cheopis</i>	Fever, headache, myalgias with transient truncal maculopapular exanthem	Doxycycline or chloramphenicol
<b>Scrub Typhus (Mite-borne typhus)</b>	<i>R. tsutsugamushi</i> (now <i>Orientia</i> ) Vector: chigger mites <b>Trombiculid</b> (larval stage)	Headache, chills, malaise and eschar at site of inoculation with lymphadenopathy → maculopapular rash on trunk, ± pulmonary and cardiac problems	Doxycycline or chloramphenicol
<b>Ehrlichiosis (Monocytic (M) Ehrlichiosis) (Granulocytic (G) Ehrlichiosis)</b>	<i>E. chaffeensis</i> (M) <i>E. phagocytophilia</i> (G) Vector: tick <i>Amblyoma americanum</i> (M); <i>Ixodes scapularis</i> , <i>Ixodes pacificus</i> (G)	Highly variable exanthem	Tetracycline or doxycycline
<b>Q Fever</b>	<i>Coxiella burnetii</i>	No skin findings; limited febrile illness, severe headache, ± pneumonia, hepatitis, endocarditis	Doxycycline



**SPIROCHETES**

- Gram-negative bacteria with spiral-shaped cells, which move via twisting motion (due to axial filaments in the flagella)
- Include *Treponema* spp., *Borrelia* spp., and *Leptospira* spp.

**Table 4-8 Select Spirochete Infections**

Disease	Organism/Vector	Clinical Findings	Treatment
<b>Lyme disease</b>	<p><i>B. burgdorferi</i></p> <p>Vector: tick</p> <p>Eastern USA, Great Lakes: <i>Ixodes dammini</i> (also known as <i>I. scapularis</i>)</p> <p>Western US: <i>Ixodes pacificus</i></p> <p>Europe: <i>Ixodes ricinus</i> (reservoir: white-footed mouse)</p> <p>Tick feeds on infected host (white footed mice, white tailed deer) → transmission to humans via infected tick saliva</p>	<p>Early localized disease: flu-like symptoms + <b>erythema migrans</b>: expanding erythematous patch at site of tick bite with central clearing, occurs ~1–2 weeks after tick bite, average diameter 5 cm, disappears typically within 4 weeks without treatment</p> <p>Early disseminated disease: oval-shaped widespread patches (satellite erythema migrans lesions) due to spirochetemia, neural involvement (facial nerve common), migratory joint pain, carditis</p> <p>Chronic disease: persistent neurologic and rheumatologic symptoms, <b>acrodermatitis chronica atrophicans</b>: loss of subcutaneous fat with thin, atrophic skin</p>	<p>Diagnosis: PCR, tissue culture, serologic evidence</p> <p>Treatment: Adults, children (&gt;8 years old): <b>Doxycycline</b> × 14–21 days, Pregnant women, children (&lt;8 years old): <b>Amoxicillin</b> × 14–21 days</p>
<b>Borrelial lymphocytoma</b> (Lymphocytoma cutis)	<p><i>B. afzelii</i></p> <p><i>B. garinii</i> (neither present in North America – only Europe)</p>	Firm bluish-red tumor or plaque appears most commonly on ear lobes of children or nipple/areolae in adults, less commonly involves genitalia, trunk, or extremities	Doxycycline
<b>Relapsing fever</b> (Louse-borne)	<p><i>B. recurrentis</i></p> <p>Vector: body louse <i>Pediculus humanus var. coporis</i></p>	Paroxysmal fevers, myalgias, no specific cutaneous findings	Doxycycline
<b>Relapsing fever</b> (Tick-borne)	<p><i>B. parkeri</i>, <i>B. hermsii</i></p> <p>Vector: soft ticks <i>Ornithodoros</i></p>	Same as louse-borne relapsing fever Risk of Jarisch–Herxheimer reaction	Doxycycline
<b>Leptospirosis</b> (For Bragg fever) (Pretibial fever) (Weil disease)	<p><i>Leptospira interrogans</i></p> <p>Direct skin contact with water contaminated by urine of infected animal</p>	Fever, headache, <u>painful pretibial plaques</u> , conjunctivitis, jaundice, ± diffuse exanthem	Pencillin (macrolides and doxycycline also effective)

**Table 4–9 Non-Veneral Treponemal Infections**

Disease	Organism/Transmission	Clinical Findings
<b>Yaws</b> (Frambesia)	<i>Treponema pallidum</i> (subspecies <i>pertenue</i> )  <u>Transmission</u> : direct contact with infectious lesions	<ul style="list-style-type: none"> <li>– <u>Primary</u>: one to few erythematous papules at inoculation site (“mother yaw”) usually on lower leg of child → enlarges, ulcerates and disappears with resultant scar</li> <li>– <u>Secondary</u>: smaller “daughter yaws” lesions spread symmetrically over body</li> <li>– <u>Tertiary</u>: skin and skeletal changes (no CNS or cardiovascular problems): gummata, keratoderma, midfacial destruction, bony inflammation and damage, nodular lesions</li> </ul> <p>Of note, mucosal yaws appear similar to condyloma lata</p>
<b>Pinta</b> (Carate)	<i>Treponema carateum</i>  <u>Transmission</u> : direct contact with infectious lesions (± possible insect vectors)	<ul style="list-style-type: none"> <li>– <u>Primary</u>: smooth papule at inoculation site</li> <li>– <u>Secondary</u>: small psoriasiform yellowish-brown papules and plaques (pintids)</li> <li>– <u>Tertiary</u>: depigmented vitiligo-like lesions over face, wrists, trochanteric areas</li> </ul>
<b>Endemic syphilis</b> (Bejel)	<i>Treponema pallidum</i> (subspecies <i>endemicum</i> )  <u>Transmission</u> : direct skin contact	<ul style="list-style-type: none"> <li>– <u>Primary</u>: skin lesions rare</li> <li>– <u>Secondary</u>: mucosal lesions including mucous patches, condylomata lata, and lymphadenopathy, ± osteitis, periostitis, bony damage, gummata (CNS and cardiovascular problems very rare)</li> </ul>
<p><b><u>Treatment for venereal and non-venereal treponematoses:</u> 2.4 million units of <b>benzathine PCN</b></b></p> <p>If PCN-allergic, can use doxycycline in same dosage as for venereal syphilis</p>		

**Syphilis (Lues, Venereal Syphilis)** (Figure 4.15 and 4.16A–C)

- Chronic systemic infection caused by *Treponema pallidum* (subsp. *pallidum*), involving multiple organs including skin, cardiac, neurologic, and skeletal system
- Transmission can be sexual (contact with infectious lesion), transplacental, or from blood products (rare)
- Clinical stages divided as follows:
- **Primary stage**
  - Chancre: localized infection at inoculation site presenting as highly infectious, indurated, painless erosion or ulceration; spontaneous resolution within 1–2 months, ± regional lymph node enlargement



**Figure 4.15**  
**Primary syphilis**  
(Courtesy of Dr. Paul Getz)

- **Secondary stage:** begins approximately 9 weeks after initial infection; specific exanthems and enanthems called syphilids
  - Exanthem: monomorphic macular or maculopapular lesions on trunk/ extremities including palms and soles with ham or copper color (can resemble pityriasis rosea or lichen planus)
  - Condyloma lata: moist papular syphilids in genital area at mucocutaneous junction
  - Lues maligna: rare form, necrotic papulopustular lesions which ulcerate with dirty crust; fever, chills
  - Alopecia: localized, diffuse, or “moth-eaten” pattern
  - Mucous patches: silver to gray superficial erosions typically involving the tongue, palate, or lips
- **Tertiary stage:** begins approximately 3–5 years after secondary syphilis
  - Gummata (singular gumma): syphilitic granulomas involving skin, oral cavity, and/or bones
  - Cardiovascular syphilis
  - Neurosyphilis: tabes dorsalis, Argyll Robertson pupil
- Serology: two types (nonspecific and specific to bacterium)
- Nontreponemal tests: become nonreactive over time and after treatment
  - **RPR** (rapid plasma reagin): detects IgM/IgG antibodies against “reagin,” a purified mixture of lipids including cardiolipin, lecithin, and cholesterol; used as screening test and also to track progress/response to therapy; expressed as titer
  - **VDRL** (Venereal Disease Research Laboratory test): same antigen as RPR
  - RPR/VDRL may not be reactive in primary syphilis until at least 1 week after chancre appears
  - False positive result may be seen with certain viral infections, immunizations, lymphoma, autoimmune disease (i.e., lupus), pregnancy, malaria, and increasing age
- Treponemal tests: most often reactive for life
  - **FTA-ABS** (fluorescent treponemal antibody absorption test): usually positive by third week of infection, remains positive after treatment, most sensitive test in primary syphilis
  - False positive: rare
- Treatment:
  - Single dose of IM benzathine PCN G 2.4 million IU (if PCN allergic: use TCN, doxycycline, or azithromycin)
  - Jarisch–Herxheimer reaction: febrile systemic reaction after initial dose of antisyphilitic treatment in about 75% patients



**Figure 4.16**

**A: Secondary syphilis\***

**B: Secondary syphilis\***

**C: Secondary syphilis, mucous patches\***

*\*Courtesy of Dr. Paul Getz*

**Table 4-10 Venereal Bacterial Infections (Figure 4.17A–F)**

Disease	Organism	Clinical Findings	Treatment
<b>Chancroid</b> (Soft chancre)	<i>Haemophilus ducreyi</i>	Soft, <b>painful</b> non-indurated ulcer with purulent base, raised and ragged borders, painful inguinal adenitis (buboes) with suppuration often present, does not heal without treatment  Gram stain: “ <b>school of fish</b> ” pattern	<b>Azithromycin</b> 1 g × 1 or <b>Ceftriaxone</b> IM × 1 or Cipro 500 mg bid × 3 days
<b>Granuloma inguinale</b> (Donovanosis)	<i>Calymmatobacterium granulomatis</i> (related to <i>Klebsiella</i> spp.)	Painless subcutaneous papule or nodule → ulcerates with <b>painful, beefy red granulation tissue</b> and serpiginous borders, rare lymphadenopathy; does not heal without treatment  Histo: <b>Donovan bodies</b>	For <b>3 weeks</b> : <b>Azithromycin</b> 1 g qweek or Bactrim DS bid or Cipro 750 mg bid or Doxy 100 mg bid
<b>Lymphogranuloma venereum</b> (Tropical bubo)	<i>Chlamydia trachomatis</i> (L1–3 serotypes)	<b>Stage I</b> : papule → painless, flast, small ulcer with gray base and serous discharge <b>Stage II</b> : enlarged unilateral inguinal lymph node (bubo) which often ruptures with suppuration, ± groove sign (if bubo above and below Poupart ligament) Giemsa stain: <b>Gamma-Favre bodies</b>	For <b>3 weeks</b> : Azithromycin 1 g qweek or Erythromycin qid or Levo 500 mg qd or <b>Doxycycline</b> 100 mg bid
<b>Gonorrhea</b>	<i>Neisseria gonorrhoeae</i>	Broad spectrum of disease patterns <b>Men</b> : gonococcal urethritis with dysuria and extensive urethral discharge of pus <b>Women</b> : urethritis and purulent cervicitis <b>Ascending gonorrhea</b> : acute salpingitis or pelvic inflammatory disease (PID) <b>Disseminated gonococcal infection</b> : episodic fever, arthralgias, tenosynovitis, swollen joints (wrists, ankles, knees commonly) and pustular hemorrhagic skin lesions	<b>Azithromycin</b> 1 g × 1 or Ceftriaxone IM × 1 or Cipro 500 mg × 1 or Doxycycline 100 mg bid × 1 week





**Figure 4.17**

**A: Granuloma inguinale\***

**B: Granuloma inguinale\***

**C: Gonococcal urethritis\***

**D: Gonococcal urethritis\***

**E: Chancroid\***

**F: Lymphogranuloma venereum\***

*\*Courtesy of Dr. Paul Getz*

## C. MYCOBACTERIA

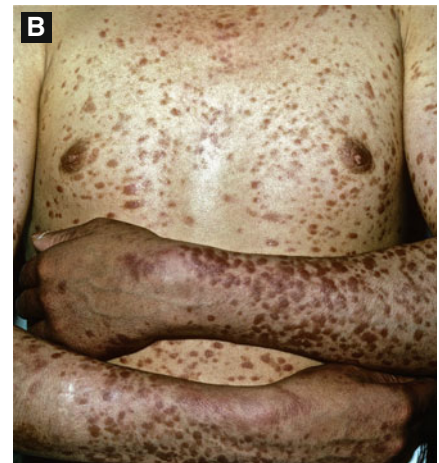
- Obligate, acid-fast, aerobic intracellular filamentous bacteria with a waxy coating

### Tuberculosis (TB) (Figure 4.18A)

- Multiorgan infection due to *Mycobacterium tuberculosis*
- Transmitted via saliva droplets, inhalation, or inoculation
- BCG: vaccination with attenuated *M. bovis*, can cause complications: tuberculids, lupus vulgaris, scrofuloderma, regional lymphadenitis
- Several manifestations of cutaneous TB (see Table 4-11)
- PPD: positive 2–10 weeks after exposure
- Histology: epithelioid granulomas with caseation necrosis
- Treatment for 2 months with multiple drugs: rifampin, isoniazid (INH), pyrazinamide, rifapentine, and/or ethambutol

### Leprosy (Hansen's Disease) (Figure 4.18B)

- Deforming and stigmatizing chronic granulomatous disease caused by *M. leprae*, which affects primarily skin and peripheral nerves
- Incubation typically 3–5 years, but can be 20+ years
- Transmission primarily via respiratory droplets
- Cellular immunity crucial for elimination of *M. leprae*
- Classification of disease based on host's level of cell-mediated immunity (see Table 4-12)
  - LL (lepromatous leprosy) ↔ BL (borderline lepromatous) ↔ BB (mid-borderline) ↔ BT (borderline tuberculoid) ↔ TT (tuberculoid leprosy)
  - Of note, patients can move through spectrum of disease via upgrading and downgrading reactions
- Reactional states: immunologically mediated inflammatory states occurring spontaneously or after initiation of treatment (see Table 4-13)
- Diagnosis
  - Acid-fast bacilli in tissue sections or smears using Fite-Faraco stain; in LL, macrophages loaded with bacteria and have foamy appearance (*Virchow cell*), in TT epithelioid tubercles surrounded by lymphocytes
  - No culture medium for *M. leprae* (can only be grown in mouse foot pad or nine-banded armadillo)
- Treatment (WHO recommendation)
  - Multibacillary → 12-month duration: dapsone 100 mg daily, clofazamine 50 mg daily and 300 mg monthly, rifampin 600 mg monthly
  - Paucibacillary → 6-month duration: dapsone 100 mg daily, rifampin 600 mg monthly
  - Of note, patients are no longer infectious after first or second dose of rifampin



**Figure 4.18**

**A: Scrofuloderma**

(Courtesy of Dr. Paul Getz)

**B: Lepromatous leprosy**

(Courtesy of Dr. Paul Getz)

**C: Erythema nodosum leprosum**

(Courtesy of Dr. Paul Getz)



**Table 4-11 Cutaneous Tuberculosis**

Disease	Clinical Findings	Immunity/Route
<b>Scrofuloderma</b>	Deep nodule typically over cervical lymph node → turns fluctuant and suppurative → ulcerates  Heals with prominent scarring	<u>Immunity</u> : sensitized host (low immunity)  <u>Route</u> : <b>contiguous spread</b> (from underlying lymphadenitis)
<b>Tuberculous chancre</b>	Painless red-brown papule at inoculation site → nonhealing, nontender undermined ulcer with painless regional lymphadenopathy	<u>Immunity</u> : non-sensitized (no prior immunity)  <u>Route</u> : <b>exogenous</b> (direct inoculation); primary infection
<b>Tuberculosis verrucosa cutis</b> (Warty TB)	Small indurated hyperkeratotic papule over hand, ankle, or buttock → warty plaque with serpiginous borders  Spontaneous resolution with scarring	<u>Immunity</u> : sensitized host (moderate to high immunity)  <u>Route</u> : exogenous (direct inoculation at site of trauma); reinfection
<b>Lupus vulgaris</b>	Gelatinous reddish-brown nodules involving face or neck with brown-yellow color (“ <b>apple-jelly</b> ”) <b>on diascopy</b>	<u>Immunity</u> : sensitized host (moderate to high immunity)  <u>Route</u> : hematogenous, lymphatic or contiguous
<b>Tuberculosis cutis orificialis</b>	Painful erythematous papule → ulcerates with undermined borders; typically in oral cavity (but can also be genitourinary)	<u>Immunity</u> : sensitized host (impaired cellular immunity)  <u>Route</u> : autoinoculation from underlying visceral infection
<b>Miliary tuberculosis</b>	Tiny bluish-red papules (teeming with bacilli) which become crusted; seen mainly infants or immunosuppressed patients	<u>Immunity</u> : nonsensitized (low immunity)  <u>Route</u> : <b>hematogenous</b> dissemination
<b>Tuberculous gumma</b>	Firm, deep seated nodule over trunk, face, or extremities → turns soft and fluctuant → ± ulceration	<u>Immunity</u> : immunosuppressed host  <u>Route</u> : hematogenous
<b>Papulonecrotic tuberculid</b>	Dusky erythematous papule → central necrosis and crust formation	<u>Immunity</u> : sensitized  <u>Route</u> : hypersensitivity reaction to distant focus of TB (tuberculid)
<b>Lichen scrofulosorum</b>	Lichenoid tiny papules (tuberculids)	
<b>Erythema induratum</b> (Bazin disease)	Subcutaneous inflammatory nodules with ulceration on <u>posterior calves</u>	Associated with past or active TB

**Table 4-12 Spectrum of Leprosy**

Tuberculoid Leprosy (TT)	Borderline Leprosy	Lepromatous Leprosy (LL)
T <sub>H</sub> 1 response (IL-2, IFN $\gamma$ , IL-12)	BL, BB, BT	T <sub>H</sub> 2 response (IL-4, IL-10)
↑ Cell-mediated immunity (intact CMI allows localization of infection)		↓ Cell-mediated immunity (lack of CMI allows progression of infection)
CD4+ cell predominance	↔	CD8+ cell predominance
↓↓ Viable organisms (paucibacillary)		↑↑ Viable organisms (multibacillary)
<b>Clinical presentation:</b> One to few well-demarcated erythematous slow-growing plaques with central clearing; lesions typically become anesthetic, anhidrotic, and hypopigmented  Tender, thickened nerves (predilection for superficial nerves with cooler temperature)  May present with neural involvement alone	Features of both	<b>Clinical presentation:</b> Poorly defined symmetric skin-colored to erythematous macules, papules, nodules, and/or plaques; dermal infiltration leads to: face → “leonine facies” eyebrows → lateral alopecia (madarosis)  Enlarged peripheral nerves, “stocking/glove” anesthesia  Testicular infection → sterility  Lagophthalmos and corneal anesthesia

**Table 4-13 Leprosy Reactional States (Figures 4.18C and 4.19A)**

Reaction	Pathogenesis	Clinical Findings	Treatment
<b>Type 1 Reaction</b> Reversal reaction	Change in cell-mediated immunity in BL patients: <u>upgrading</u> to more resistant state (↑ destruction of bacilli) or <u>downgrading</u> to less resistant state	– <u>Upgrading</u> : skin lesions become <b>acutely inflamed</b> , rare new lesions; neuritis with rapid-onset pain, swelling, tenderness, and loss of function of affected nerves – <u>Downgrading</u> : lesions acutely inflamed, new lesions; neuritis	<b>Systemic corticosteroid</b> (40 mg to 80 mg) and taper over several weeks
<b>Type 2 Reaction</b> Erythema nodosum leprosum (ENL)	Upgrading reaction in BL and LL patients during treatment: ↑ antibody levels leads to immune complex deposition in vessels → <b>small vessel vasculitis</b>	Presents with deep, painful erythematous nodules on face or trunk  Fever, malaise, neuritis, iridocyclitis, arthralgias	<b>Thalidomide</b>  Clofazamine and systemic corticosteroid may also be added
<b>Type 3 Reaction</b> Lucio reaction	Extensive, <b>severe vasculitis</b> in untreated LL patients	Presents with pink, painful hemorrhagic or necrotic nodules, ± ulceration, bulla formation, eschars	Systemic corticosteroid

Of note, always continue antimycobacterial treatment when treating leprosy reactions



## ATYPICAL MYCOBACTERIA

- Also known as nontuberculous mycobacteria (mycobacteria other than those causing TB and leprosy)
- Found naturally in the environment (water and soil)
- Transferred via dust, skin injuries, droplets, and occasionally cause opportunistic infections
- Ziehl–Neelson stain; Lowenstein–Jensen culture medium

### *M. marinum* (Fish Tank Granuloma) (Figure 4.19B)

- Infection follows traumatic inoculation during exposure to an aquatic environment where *M. marinum* resides as a normal saprophyte (lakes, fish tanks, etc.)
- Presents as a slow-growing blue-red papule at the site of inoculation, ± ascending lymphatic sporotrichoid spread; immunosuppressed patients with disseminated lesions
- Diagnosis: tissue culture (grows in 2–4 weeks at 32°C, not 37°C), biopsy suggestive (not pathognomonic)
- Treatment: minocycline, doxycycline, trimethoprim-sulfamethoxazole, or clarithromycin for at least 1–2 months after resolution

### *M. ulcerans* (Buruli Ulcer) (Figure 4.19C)

- Produces indolent ulcers after minor trauma, associated with agricultural activities
- Presents as nontender deep-seated nodule which ulcerates, forming deep necrotic base with undermined borders; ± osteomyelitis if underlying bone involved
- Treatment: excision, local heat (as bacteria prefer cooler temperatures); drug therapy often disappointing

### *M. fortuitum* Complex

- Complex includes *M. chelonae*, *M. fortuitum*, *M. abscessus*; saprophytes in soil and water
- Presents typically as either postinjection cold abscess or furunculosis

### *M. avium*-Intracellulare Complex (*M. avium* Complex, MAI)

- Common opportunistic infection in patients with AIDS
- Chronic pulmonary infection; rare skin involvement

### *M. kansasii*

- Photochromagen (“yellow” bacillus), natural reservoir is water; transmission via minor trauma
- Presents as verrucous plaques, nodules, or ulcers in immunocompromised persons

Of note, other photochromagens (pigmentation on exposure to light): *M. marinum*, *M. simiae*



**Figure 4.19**

**A: Erythema nodosum leprosum, arm**  
(Courtesy of Dr. Paul Getz)

**B: Fish tank granuloma**

**C: Buruli ulcer**  
(Courtesy of CDC)

### 4.3 FUNGAL INFECTIONS

- Classified into: superficial (invade stratum corneum, hair, and nails), subcutaneous (usually due to implantation) and deep (systemic) infection
- Further subdivided into true and opportunistic pathogens

#### A. DEFINITIONS

- Yeast:** unicellular fungus, round to ovoid organisms with asexual reproduction (budding or binary fission), pseudohyphae (long chain of yeast cells with constrictions rather than true septae), form moist colonies
- Mold:** multicellular filamentous fungus with hyphae (tubular branching cells, regular septae), reproduction via spore development and dispersal; can be geophilic (growth primarily in soil), zoophilic (predominantly infects animals), or anthrophilic (infects humans), cell membrane with unique sterol (ergosterol)
  - Dimorphic fungi:** grow as either yeast or mold, depending on environmental conditions (yeast form in tissue at 37°C, but mycelial form in environment at 25°C)
  - Dematiaceous fungi:** fungi with pigmented hyphae (green, brown, or black); appearance of brown-black coloration on artificial culture media
- Mycelium:** large intertwined mass of hyphae; different types (see below)

Types of Mycelia	
<b>Spiral hyphae</b>	Regular hyphae with occasional spiral coils ( <i>T. mentagrophytes</i> )
<b>Pectinate bodies</b>	Hyphal ends with protuberances resembling comb ( <i>M. audouinii</i> )
<b>Nodular bodies</b>	Knot of twisted hyphae
<b>Racquet hyphae</b>	Hyphae with club-shaped cells ( <i>C. immitis</i> )
<b>Favic chandeliers</b>	Hyphae terminate in broad branches resembling antlers ( <i>T. schoenleinii</i> )

- Spores:** reproducing bodies of fungi; asexual or sexual
  - Asexual spores: often characteristic for particular species, thus used as basis for identification; two types: sporangiospores and conidia
    - Conidia:** free spores produced directly from hyphae or supporting conidiophores, different types

Types of Asexual Conidia	
<b>Arthroconidia</b>	Barrel-shaped spores released by fragmentation of hyphae ( <i>C. immitis</i> )
<b>Chlamydoconidia</b>	Spherical, thickened, resistant hyphal cell ( <i>C. albicans</i> , <i>T. tonsurans</i> )
<b>Microconidia</b>	Small asexual spores
<b>Macroconidia</b>	Large leaf or club-shaped asexual spores
<b>Blastoconidia</b>	Conidia formed by budding

Of note, macro- and microconidia may be found on branches of same mycelium filament

## Direct Stains

- **Potassium hydroxide (KOH)**: dissolves keratin but leaves behind the hyphae (faster if dimethyl sulfoxide [DMSO] added)
- **Chlorazol black E**: chitin-specific blue-black stain
- **Calcofluor**: colorless dye, binds cellulose and chitin in fungal cell walls, seen under fluorescent microscope (apple-green fluorescence)

## Histology

- **Gomori methenamine silver (GMS)**: outlines fungal elements black
- **Periodic acid-Schiff (PAS)**: outlines fungal elements magenta with green background
- **Fontana-Masson**: stains dematiaceous fungi
- **Mucicarmine**: stains capsule of *Cryptococcus neoformans* pink

## Media (Figure 4.20A–C)

- **Sabouraud Dextrose Agar (SDA)**: gold standard (peptone, glucose, water, agar)
- **Modified SDA** (Mycosel or Mycobiotic): SDA + cycloheximide + chloramphenicol
  - Cycloheximide inhibits saprophytic fungi (*Prototheca*, *H. werneckii*, *Scytalidium*, *Candida other than albicans*, *C. neoformans*)
  - Chloramphenicol inhibits bacteria
- **Dermatophyte Test Medium (DTM)**: peptones, dextrose, cycloheximide, phenol red, chlortetracycline, and gentamicin
  - Dermatophytes turn media from amber to red color due to alkaline by-products
  - Non-dermatophytes cause media to turn yellow (or stay amber-colored)

## B. SUPERFICIAL MYCOSES

- Includes only fungi invading keratinized tissues (hair, nails, stratum corneum)
- Divided into noninflammatory (tinea versicolor, tinea nigra, piedra) and inflammatory (dermatophytosis, candidiasis)

## Pityrosporum Folliculitis (Malassezia Folliculitis)

- On rare occasions, *M. furfur* may infect hair follicles
- Presents as monotonous acne-like folliculocentric papules typically over back, occasionally evolving into pustules → heal with brown, easily removed crust
- Treatment: topical imidazole, fluconazole 400 mg × 1 or ketoconazole 400 mg



**Figure 4.20**

**A:** DTM, non-dermatophyte\*

**B:** DTM, dermatophyte\*

\*Courtesy of Hardy Diagnostics,

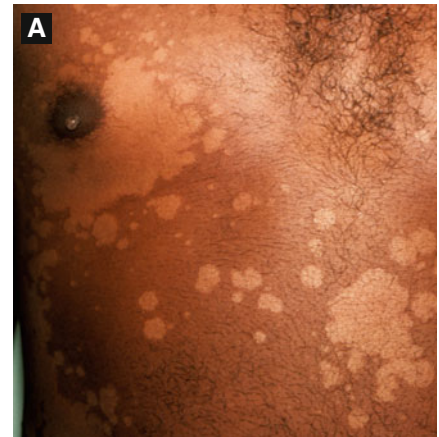
[www.HardyDiagnostics.com](http://www.HardyDiagnostics.com)

**C:** DTM, non-dermatophyte (left) and dermatophyte (right)

(Courtesy of Sandra Arduin, Michigan Department of Community Health)

**Tinea Versicolor (Pityriasis Versicolor)** (Figure 4.21A)

- *Malassezia furfur* (yeast form: *Pityrosporum ovale* or *P. orbiculare*)
- Yeast part of normal cutaneous flora, but pathogenic when transforms into mycelial form; requires lipid enrichment when growing
- *M. furfur* produces azelaic acid (a dicarboxylic acid) → blocks melanin synthesis causing ↓ pigmentation
- Presents as hyper- and hypopigmented macules and patches with fine scale in lipid-rich areas of skin; common in summer; facial lesions common in infants
- KOH: “ziti and meatballs” (short, thick hyphae with grape-like spores); culture requires lipid enrichment (olive oil overlay); Wood’s light shows pale yellow fluorescence
- Treatment: topical imidazoles, selenium sulfide, zinc pyrithione, or oral ketoconazole 400 mg qweek × 2 doses

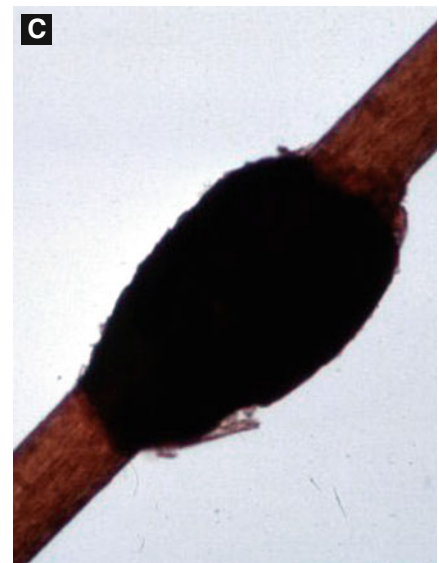
**Tinea Nigra** (Figure 4.21B)

- Dematiaceous fungus: *Hortaea werneckii* (formerly known as *Exophiala werneckii*, *Phaeoannellomyces werneckii*, and *Cladosporium werneckii*)
- Geophilic: transmission likely acquired via direct contact with soil or decaying vegetation
- Presents as one or more sharply demarcated hyperpigmented to gray macules or patches with fine scale on the palms or soles; can be mistaken for melanoma (but former has advancing border with darker pigmentation compared to center)
- Pigment within stratum corneum (scrapes off easily) and golden brown hyphae seen on KOH; black shiny colony on culture
- Treatment: topical imidazoles or allylamines

**Piedra** (Figure 4.21C)

- Superficial infection of hair shaft where fungal elements adhere to form nodes along hair shaft
- Two types: black piedra and white piedra
  - **Black piedra:** *Piedraia hortae*; presents with tiny dark concretions on hairs shafts distributed irregularly; culture shows black velvety colony
  - **White piedra:** *Trichosporon cutaneum* (formerly *T. beigellii*) most common; other species include *T. ovoides*, *T. inkin*, and *T. asahii*; presents with light brown, less adherent nodules coating hair shaft (beard, axilla, pubic hairs)
- Of note, *T. cutaneum* can cause fungemia with systemic disease in immunocompromised patients
- Treatment: shaving/cutting hair, topical imidazoles

Do not confuse trichosporon with “trichophyton”

**Figure 4.21****A: Pityriasis versicolor**

(Courtesy of Dr. Paul Getz)

**B: Tinea nigra**

(Courtesy of Dr. Marcus Henrique de Sousa Brito Xavier, Brazil)

**C: Piedra**(Courtesy of Doctor Fungus, [www.doctorfungus.org](http://www.doctorfungus.org))



## DERMATOPHYTOSIS

- Three genera of fungi with capability of invading keratinized tissue: *Microsporum*, *Trichophyton*, and *Epidermophyton*
- Dermatophytes may produce keratinolytic enzymes (such as keratinase), which allows for the breakdown of keratin
- Sebum has an inhibitory effect of dermatophytes

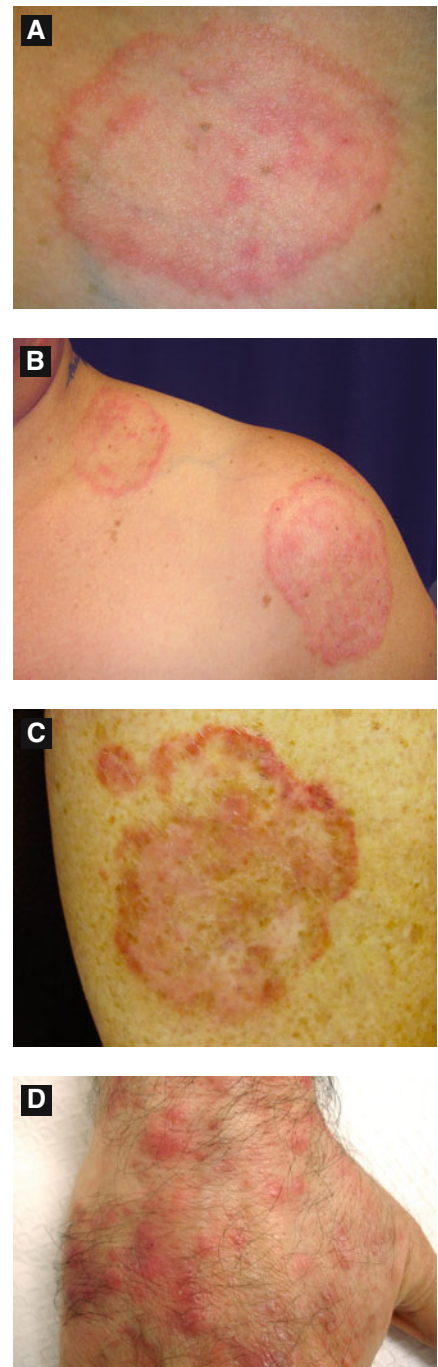
### Tinea Corporis (Figure 4.22A–D)

- *T. rubrum* most common; may spread from fungal infection of feet (*T. rubrum*, *T. mentagrophytes*), infected animal (*M. canis*), or soil (*M. gypseum*)
- Presents as erythematous, sharply marginated, scaly plaque with raised, advancing border; typically with central clearing and annular or arcuate shape
- Clinical variants
  - **Tinea imbricata:** *T. concentricum*, presents with distinct scaly plaques arranged in concentric rings
  - **Tinea profunda:** marked inflammatory response to a dermatophyte (analogous to kerion on scalp)
  - **Tinea incognito:** dermatophyte infection without obvious signs of inflammation (usually due to prior treatment with topical corticosteroid)
  - **Majocchi's granuloma:** *T. rubrum* (most common), granulomatous folliculitis due to dermatophyte entering hair follicles (usually due to prior topical corticosteroid use), treat with oral antifungal
- Treatment: topical therapy usually adequate (imidazole, allylamine); if extensive or involving hair follicles can use oral terbinafine or itraconazole

### Tinea Cruris

- Erythematous patch typically with raised, serpiginous scaly border and central clearing involving upper inner thighs and crural folds; scrotum rarely involved
- Treatment: topical antifungal cream

If scrotum involved, think candidiasis



**Figure 4.22**

A: Tinea corporis

B: Tinea corporis

C: Majocchi's granuloma, leg

D: Majocchi's granuloma, hand

**Tinea Barbae (Tinea Sycosis) (Figure 4.23A)**

- Uncommon infection of hair caused by *M. canis*, *T. mentagrophytes*, or *T. verrucosum*
- Presents as painful inflammatory nodular swellings typically involving beard or moustache area
- Treatment: oral antifungal

**Tinea Faciei (Figure 4.23B, C)**

- Seen more commonly in children with *T. rubrum*, *T. mentagrophytes*, or *M. canis*
- Erythematous serpiginous plaques with scaling on face, sometimes annular
- Treatment: topical antifungal cream (oral antifungal treatment if any follicular involvement)

**Tinea Capitis (Figures 4.23D and 4.24A)**

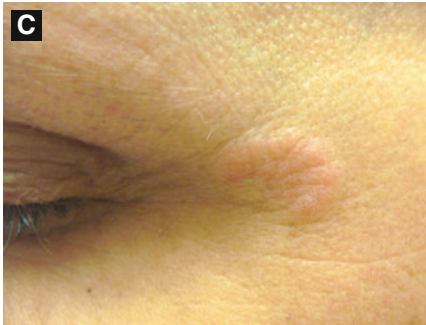
- Common dermatophyte infection in scalp of children
- Two types: endothrix and ectothrix
- *T. tonsurans* (endothrix) most common cause; second most common is *M. canis* (highly inflammatory) and *M. audouinii*
- **Ectothrix:** fungal spores coat outside of hair and cuticle destroyed; may or may not fluoresce with Wood's light (365 nm, mercury lamp with nickel chromium oxide filter)

Fluorescent ectothrix	Nonfluorescent ectothrix
<i>M. canis</i>	<i>T. mentagrophytes</i>
<i>M. audouinii</i>	<i>T. verrucosum</i>
<i>M. distortum</i>	<i>T. rubrum</i>
<i>M. ferrugineum</i>	<i>T. megnini</i>
<i>M. gypseum</i> (sometimes)	<i>M. nanum</i>
<i>T. schoenleinii</i>	

Fluorescent: Cats And Dogs Fight and Growl Sometimes (due to pteridine)

- **Endothrix:** spores within hair shaft, cuticle intact, hairs can break at surface (“black dot” tinea)
  - *T. rubrum* (causes both endo/ecto), *T. gourvilli*, *T. yaounde*, *T. tonsurans*, *T. soudanense*, *T. violaceum*

Endothrix: Ringo Gave Yoko Two Squeaky Violins



**Figure 4.23**  
**A: Tinea barbae**  
(Courtesy of Dr. Marcus Henrique de Sousa Brito Xavier, Brazil)  
**B: Tinea faciei**  
(Courtesy of Dr. Paul Getz)  
**C: Tinea faciei**  
**D: Tinea capitis**  
(Courtesy of Dr. Paul Getz)

- **Favus:** rare variant of endothrix with yellow cup-shaped crusting (scutula) on scalp; arthroconidia and airspaces within hair shaft
  - *T. schoenleinii*, *T. violaceum*, *M. gypseum*
- **Kerion:** variant of endothrix with boggy inflammatory plaques, ± scarring alopecia
- Treatment: oral antifungal for at least 2 months

### Tinea Pedis (Figure 4.24B)

- Commonly due to *T. rubrum* (relative noninflammatory)
- Different types
  - **Moccasin type** (*T. rubrum*, *E. floccosum*): dull erythema with scaling involving sole and sides of foot, may be focal
  - **Bullous type** (*T. mentagrophytes*): multilocular bullae often located along the instep (arch)
  - **Interdigital type** (*T. rubrum*, *T. mentagrophytes*): erythema, maceration, and fissuring of the webspace
- Dermatophytid (“id”) reaction of the hands may occur due to inflammatory tinea pedis
- Treatment: topical antifungal, if extensive use oral terbinafine 250 mg qd×2 weeks

### Onychomycosis (Figure 4.24C)

- Infection of the nail plate, most commonly due to *T. rubrum*, but also by other dermatophytes, yeast, and nondermatophytic molds
- Four types:
  - **Distal subungual onychomycosis:** involvement of distal nail bed and hyponychium; typically due to *T. rubrum*
  - **White superficial onychomycosis (WSO):** chalky white superficial infection of nail plate; mainly due to *T. mentagrophytes* (of note, *T. rubrum* more common in HIV patients)
  - **Proximal subungual onychomycosis:** least common form, presents with areas of leukonychia in proximal nail plate near lunula; usually due to *T. rubrum*; can be a sign of HIV infection
  - **Candida onychomycosis:** destruction of nail and massive nail bed hyperkeratosis, typically seen in patients with mucocutaneous candidiasis; due to *C. albicans*
- Treatment: oral terbinafine 250 mg qd×6–8 weeks for fingernails and 12–16 weeks for toenails



**Figure 4.24**  
**A: Tinea capitis**  
 (Courtesy of Dr. Paul Getz)  
**B: Tinea pedis, interdigital**  
**C: Onychomycosis**



## Microsporum

**Microconidia** – not distinctive

**Macroconidia** – diagnostic (rough-walled, multicelled, and barrel-shaped)

May cause both fluorescent and nonfluorescent ectothrix infections

### *M. audouinii*

- Infection: formerly #1 cause of tinea capitis in children
- Colony: gray-white color → reverse salmon-red color; “mouse fur appearance”
- Hyphae: ± **pectinate hyphae** (resembles broken comb), racquet hyphae
- Conidia: poorly shaped, thick-walled, and **barrel-shaped** and **pointed ends**
- Misc: (–) **polished rice growth**

### *M. canis* (Figure 4.25A)

- Infection: #1 cause of tinea capitis (ectothrix) worldwide, often transmitted from **cats/dogs**
- Colony: fluffy white → reverse **deep yellow**
- Hyphae: racquet hyphae, nodular bodies, chlamydospores
- Conidia: **spindle-shaped** with rough, thick walls and pointed ends (>6 cells)
- Misc: (+) **polished rice growth**, (+) **hair perforation**

### *M. ferrugineum*

- Infection: tinea corporis, tinea capitis (ectothrix)
- Colony: yellow to rusty orange → reverse rusty to beige
- Hyphae: thick straight **bamboo-like** hyphae
- Conidia: occasional chlamydospores, no conidia
- Misc: (–) hair perforation, (–) urease

### *M. gypseum* (Figure 4.25B)

- Infection: tinea capitis (ectothrix), favus
- Colony: cinnamon color → reverse yellow
- Conidia: fusiform thin-walled macroconidia with rounded ends, club-shaped microconidia
- Misc: (+) **polished rice growth**, rapid growth

### *M. nanum* (Figure 4.25C)

- Infection: pig ringworm, tinea capitis (ectothrix)
- Colony: fluffy white-beige → reverse orange to brown
- Conidia: small 1–3 celled macroconidia (“**pig snout**”)

### *M. gallinae*

- Infection: chicken favus, rare tinea capitis (ectothrix)
- Colony: pink-white → reverse **red diffuses into agar**



**Figure 4.25**

A: *M. canis*\*

B: *M. gypseum*\*

C: *M. nanum*\*

\*Courtesy of Sandra Arduin, Michigan Department of Community Health



### Trichophyton

**Microconidia** – diagnostic

**Macroconidia** – not diagnostic

May cause both nonfluorescent ectothrix and endothrix

#### *T. mentagrophytes* (Figure 4.26A)

- **Infection:** **bullous tinea pedis**, tinea corporis, tinea barbae, white superficial onychomycosis, tinea capitis (ectothrix)
- **Colony:** fluffy white to buff → reverse red to brown
- **Hyphae:** **spiral hyphae** (black arrow)
- **Conidia:** cigar-shaped, thin-walled microconidia
- **Misc:** (+) **hair perforation**, (–) pigmentation on cornmeal agar, (+) urease

#### *T. rubrum* (Figure 4.26B)

- **Infection:** **most common dermatophyte**; tinea pedis, tinea corporis, onychomycosis, **Majocchi's granuloma**
- **Colony:** fluffy white → reverse red (no diffusion)
- **Hyphae:** septate hyphae
- **Conidia:** **teardrop-shaped** microconidia resembling “birds on a wire,” pencil-shaped macroconidia rare
- **Misc:** (–) **hair perforation**, (+) pigmentation on cornmeal agar, (–) urease

#### *T. soudanense*

- **Infection:** tinea capitis (endothrix)
- **Colony:** apricot-colored and suede-like → reverse yellow
- **Hyphae:** septate hyphae with **reflexive branching**
- **Conidia:** teardrop-shaped microconidia

#### *T. tonsurans* (Figure 4.26C)

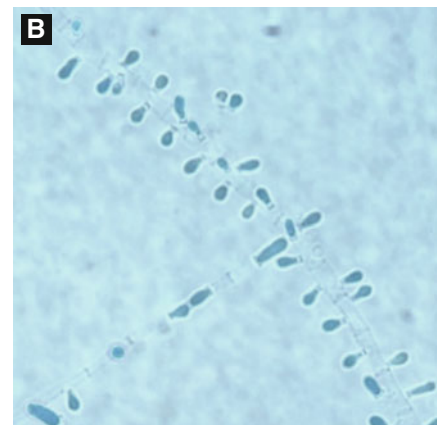
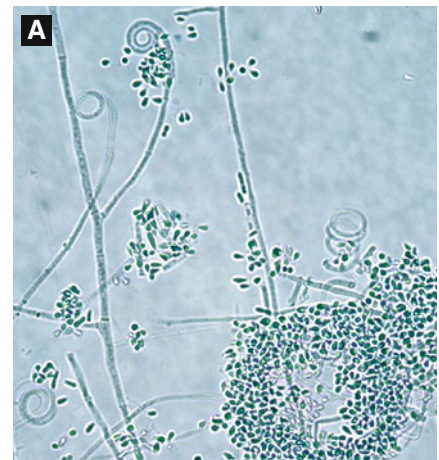
- **Infection:** **most common** cause of tinea capitis in the USA (**endothrix**), tinea corporis, tinea pedis
- **Colony:** varying color → reverse reddish brown
- **Hyphae:** septate hyphae with **spiral coils**
- **Conidia:** variable sizes (**teardrop, balloon, matchstick forms**)
- **Misc:** partial **thiamine** requirement

#### *T. schoenleinii*

- **Infection:** tinea capitis (**fluorescent endothrix**), **favus**, tinea corporis, tinea unguium
- **Colony:** cerebriform, cream-colored and grows **deep into agar** → reverse yellow to colorless
- **Hyphae:** septate hyphae with “**favic chandeliers**” (branching hyphae resemble antlers)
- **Conidia:** none

#### *T. verrucosum* (Figure 4.27A)

- **Infection:** tinea capitis (**ectothrix**), inflammatory tinea barbae, tinea corporis, tinea faciei
- **Colony:** waxy white → reverse yellow to colorless
- **Hyphae:** thick irregular hyphae
- **Conidia:** **chains** of chlamydospores (like “string of beans”)
- **Misc:** partial **thiamine and inositol** requirement, grows best at 37°C



**Figure 4.26**

A: *T. mentagrophytes*\*

B: *T. rubrum*\*

C: *T. tonsurans*\*

\*Courtesy of Sandra Arduin, Michigan Department of Community Health

***T. violaceum*** (Figure 4.27B)

- **Infection:** tinea capitis (**endothrix**), **favus**, tinea corporis, tinea barbae
- **Colony:** heaped, folded, and **deep violet** → reverse deep port wine
- **Hyphae:** **tangled, septate irregular hyphae**
- **Conidia:** few
- **Misc:** partial **thiamine** requirement

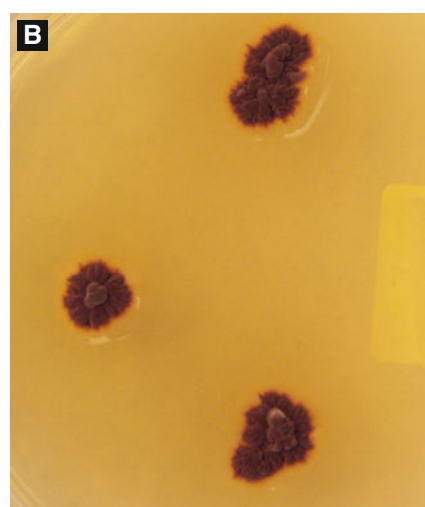
Epidermophyton	
Microconidia – none produced	No hair involvement
Macroconidia – club-shaped	

**Epidermophyton floccosum** (Figure 4.27C)

- **Infection:** tinea pedis, tinea cruris, tinea corporis, onychomycosis
- **Colony:** **khaki-colored** to olive color → reverse orange-brown
- **Hyphae:** septate hyphae
- **Conidia:** **club-shaped** 2–6 celled macroconidia occurring characteristically in clusters (“**beaver tail**”)

**Table 4-14 Fungal Growth Requirements**

Thiamine requirement	Inositol/Thiamine requirement	Histidine requirement	Nicotinic acid requirement
<i>T. violaceum</i> <i>T. concentricum</i> <i>T. tonsurans</i> <i>T. verrucosum</i>	<i>T. verrucosum</i>	<i>T. megnini</i>	<i>T. equinum</i>  Horses (equinum) are nice (nicotinic acid)
Pigmentation on cornmeal agar	Growth on polished rice	Hair perforation (penetration)	Urease activity present
+ <i>T. rubrum</i> – <i>T. mentag</i>	+ <i>M. canis</i> – <i>M. audouinii</i>	+ <i>T. mentag</i> – <i>T. rubrum</i>	+ <i>T. mentag</i> – <i>T. rubrum</i>

**Figure 4.27**A: *T. verrucosum*\*B: *T. violaceum*\*C: *E. floccosum*\*

\*Courtesy of Sandra Arduin, Michigan Department of Community Health

**Scytalidium dimidiatum**

Dematiaceous fungus (pigmented)

- **Infection:** tinea pedis, paronychia, onychomycosis
- **Colony:** woolly white (turns gray to olive brown) → reverse gray to black
- **Hyphae:** pigmented septate hyphae (hyaline to olive brown)
- **Conidia:** thin- to thick-walled round to rectangular arthroconidia
- Of note, resistant to most antifungals; sensitive to cycloheximide

**Candidiasis** (Figure 4.28)

- *C. albicans* common inhabitant of skin, GU, and GI tract
- Opportunistic organism, can become pathogen in skin, nails, and mucous membranes
- Frequently infects intertriginous areas

<b>Thrush</b> (Moniliasis)	Presents as gray-white plaques on mucous membranes with reddish macerated base and/or smooth-surfaced bright red tongue (atrophic papillae)
<b>Vulvovaginitis</b>	Overgrowth of candida causes burning, itching, discharge; associated with diabetes mellitus, antibiotic use, pregnancy
<b>Candidal intertrigo</b>	Pink to bright red moist patches, ± satellite papules/pustules in intertriginous areas (typically inframammary)
<b>Candidal paronychia</b>	Redness, tenderness, edema of nailfold; associated with chronic exposure to moisture and irritants  Of note, <u>acute</u> paronychia associated with <u>bacteria</u> , while chronic paronychia associated with yeast and irritation
<b>Perleche</b> (Angular cheilitis)	Transverse fissuring and maceration of oral commissures
<b>Diaper candidiasis</b>	Erythematous patches in groin, ± satellite papules/pustules
<b>Perineal candidiasis</b>	Perianal dermatitis with erythema, maceration, burning, and pruritus (due to mechanical chafing ± incontinence)
<b>Erosio interdigitalis blastomycetica</b>	Maceration between webspace of fingers (nearly always third web space), similar in toes but usually fourth webspace affected



**Figure 4.28**  
**Candidiasis**  
(Courtesy of Dr. Paul Getz)

## C. DEEP MYCOSES

### **Lobomycosis (Keloidal Blastomycosis)** (Figure 4.29A)

- *Lacazia loboi* (formerly *Loboa loboi*); found in Amazon basin and Gulf of Mexico; associated with dolphins
- Presents as painless smooth-surfaced nodules (resembling keloids), ± ulceration, ± verrucous appearance
- Histology: round or lemon-shaped cells attached to one another with narrow connections (“chain of coins” or “brass knuckles”); cannot be cultured
- Treatment: surgical excision (antifungals ineffective)

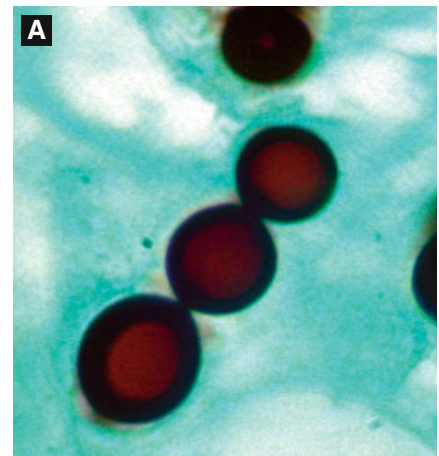
### **Eumycotic Mycetoma (Madura Foot)** (Figure 4.29B, C)

- True fungal infection (unlike actinomycetoma)
- Found in soil and plants; ↑ prevalence in Mexico, Central/South America, India, and Africa
- Commonly due to penetrating wound to foot (can also be on upper back, legs, or shoulders)
- Presents with slow progression of tumefaction, draining sinuses, and discharge of grains → scarring with deformity, ± bone involvement
- Histology: grains (aggregates of organism) admixed with chronic inflammation and fibrosis
- Treatment: oral antifungal (itraconazole, ketoconazole, griseofulvin) and debridement

Grain	Organism
White	<i>Acremonium</i> spp., <i>Aspergillus</i> spp., <i>Fusarium</i> spp.
White-yellow	<i>Pseudallescheria boydii</i>
Black	<i>Exophiala jeanselmei</i> , <i>Curvularia</i> spp., <i>Madurella</i> spp., <i>Leptosphaeria</i> spp., <i>Pyrenochaeta romeroi</i>

### **Chromoblastomycosis (Chromomycosis)**

- Five dematiaceous organisms responsible for disease: *Fonsecaea* (*Phialophora*) *pedrosoi* (most common), *Fonsecaea compacta*, *Rhinocladiella aquaspersa*, *Phialophora verrucosa*, *Cladosporium carrionii*
- Found in soil, wood, and decaying vegetation; infection with traumatic foot injury mainly in agricultural workers
- Presents with slow-growing papule → verrucous plaques with swelling, ± annular with central clearing, ± lymphedema, ± elephantiasis
- Histology: pseudoepitheliomatous hyperplasia, dematiaceous hyphae in dermis, brown thick-walled cells called Medlar bodies (also known as copper pennies or sclerotic bodies)
- Culture: gray to black velvety colony
- Treatment: surgery and/or itraconazole



**Figure 4.29**

**A:** “Brass knuckles” in lobomycosis  
(Courtesy of CDC)

**B:** Mycetoma  
(Courtesy of Dr. Paul Getz)

**C:** *Exophiala jeanselmei*  
(Courtesy of Sandra Arduin, Michigan Department of Community Health)



## DIMORPHIC FUNGI

### Sporotrichosis (Figure 4.30A)

- *Sporothrix schenckii*, dimorphic fungus found in soil, thorns, moss, and bark
- Risk factors: florist, gardener, farmer, miner, alcoholic
- Transmission via direct inoculation and inhalation (usually injury from splinter or rose thorn)
- Different forms:
  - **Lymphocutaneous:** subcutaneous nodule ± ulceration with ascending lymphatic spread
  - **Fixed cutaneous:** single subcutaneous nodule, ± ulceration, no lymphatic spread
  - **Disseminated:** rare; involves bones, joints, meninges, pulmonary, and genitourinary tract
- Pathology: sporothrix asteroid body (yeast cell with surrounding eosinophilic fringe), also known as Splendore–Hoepli phenomenon
- Colony: 25°C fluffy white → turns black; 37°C smooth cream-colored; conidia arranged in groups at end of conidiophore (flower-like) resembling daisies
- Treatment: itraconazole or supersaturated potassium iodide (SSKI) for lymphocutaneous form

### Coccidioidomycosis (San Joaquin Valley Fever) (Figure 4.30B, C)

- *Coccidioides immitis*, found in soil of southwestern USA
- Spherules have unencapsulated thick refractile wall
- Infectious arthroconidia inhaled via dust particles
- Types of presentation
  - **Pulmonary:** inhalation of infectious arthroconidia → 40% patients with flu-like symptoms, hilar adenopathy, pulmonary infiltrate, erythema nodosum (favorable prognostic sign)
  - **Disseminated:** <1% cases; targets joints, viscera, brain, skin (pink papules or deep-seated nodules frequently involving face)
  - **Cutaneous:** very rare, due to inoculation; indurated nodule that may ulcerate with sporotrichoid pattern
- Histology: spherules with double refractile, thick walls (20–80 μm) loaded with endospores; diagnostic arthrospores with colony growth showing septate hyphae with infectious, thick-walled barrel-shaped arthroconidia separated by clear spaces (remnants of empty cells)
- Treatment: oral itraconazole, ketoconazole, or fluconazole

Spherules smaller than sporangia in Rhinosporidiosis

In HIV, lesions may resemble molluscum contagiosum



**Figure 4.30**

**A: *Sporothrix schenckii***  
(Courtesy of Sandra Arduin, Michigan Department of Community Health)

**B: Coccidioidomycosis\***

**C: Coccidioidomycosis\***

\*Courtesy of Dr. Paul Getz

**Histoplasmosis (Ohio Valley Disease) (Figure 4.31A, B)**

- *Histoplasma capsulatum*, soil saprophyte, frequently in bat/bird feces which can harbor infectious fungal spores, common in southeastern and central USA; transmission via inhalation of airborne spores (soil or caves)
- Contains pseudocapsule; striking resemblance to leishmaniasis but lack kinetoplast and distributed evenly throughout the cytoplasm
- Typically results in asymptomatic primary pulmonary infection with rare skin findings in healthy patients; HIV patients can present with umbilicated papules, nodules, pustules,  $\pm$  ulceration (but oral ulcers common presentation with chronic disseminated disease)
- Histology: characteristic intracellular yeast (2–4  $\mu$ m) surrounded by rim of clearing (unstained capsule)
- Culture: white cottony colony at 25°C; moist yeast colony at 37°C; pear-shaped microconidia; round, spiny tuberculate macroconidia
- Treatment: spontaneous healing if minimal disease; amphotericin B in severely ill patients; itraconazole or ketoconazole in less severe cases

**Blastomycosis (North American Blastomycosis)**

(Figures 4.31C and 4.32A, B)

- *Blastomyces dermatitidis*, endemic in Great Lakes, Ohio river basin, and Mississippi river; found mainly in soil
- Two types:
  - **Primary pulmonary infection:** typically asymptomatic or self-limited, can turn into chronic pulmonary (mimics TB or pneumonia), 80% cases with dissemination to skin
  - **Cutaneous infection:** typically due to secondary cutaneous dissemination after pulmonary infection and variable presentation: papulopustules, well-demarcated verrucous plaques with crusting and pustules especially at border,  $\pm$  central ulceration, healing begins centrally and heals with cribriform scarring
- Histology: round yeast forms with broad-based budding (8–15  $\mu$ m), thick double-contoured wall, giant cells, and neutrophilic abscesses
- Culture: white fluffy colony at 25°C; yeast cell with double-contoured thick walls, broad base, and typical single budding at 37°C; conidia on conidiophores resembling lollipops
- Treatment: oral antifungal (itraconazole, ketoconazole), if severe or progressive use amphotericin B

**Figure 4.31****A: *Histoplasma capsulatum*, tuberculate macroconidium**

(Courtesy of Sandra Arduin, Michigan Department of Community Health)

**B: Histoplasmosis\*****C: *Blastomyces dermatitidis*\***

\*Courtesy of Dr. Paul Getz

### Paracoccidioidomycosis (South American Blastomycosis)

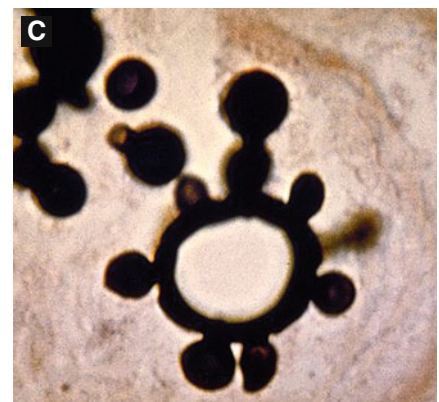
(Figure 4.32C)

- *Paracoccidioides brasiliensis*, dimorphic fungus, endemic to Central/South America
- Infection via inhalation of conidia from environment
  - **Primary pulmonary infection:** resembles pneumonia, ± dissemination to skin and other organs
  - **Cutaneous infection:** slow-growing painful verrucous or ulcerative nodules typically around mouth with painful oral and nasal mucosal ulcerations
- Histology: pseudoepitheliomatous hyperplasia, characteristic large round organism with multiple narrow-based buds radiating outward (mariner's wheel)
- Treatment: amphotericin B, oral azoles, and sulfonamides

### OPPORTUNISTIC INFECTIONS

#### Cryptococcosis (Figure 4.33A)

- *Cryptococcus neoformans*, dimorphic fungus with characteristic polysaccharide capsule, found in pigeon droppings, soil, and dust
- Transmission via inhalation
- Presentation:
  - **Primary pulmonary infection:** asymptomatic or mild infection in an immunocompetent person, but immunocompromised person may have disseminated disease (can spread to CNS, bone, skin); secondary skin lesions are polymorphous (molluscum-like umbilicated papules, acneiform pustules, papules, nodules, abscesses, etc.)
  - **Primary cutaneous infection** (inoculation): extremely rare
- Histology: encapsulated yeast (2–12 µm), ± single or budding, mucoid capsule stains well with mucicarmine, PAS, Alcian blue; India ink stains yeast (capsule appears as clear halo)
- **Gelatinous pattern:** numerous budding yeast, capsule does not stain which gives dermis vacuolated gelatinous appearance, minimal inflammation
- **Granulomatous pattern:** pseudoepitheliomatous hyperplasia, granulomatous infiltrate with fewer yeast
- Treatment: amphotericin B ± flucytosine



**Figure 4.32**

**A: Blastomycosis\***

**B: Blastomycosis\***

*\*Courtesy of Dr. Paul Getz*

**C: *Paracoccidioides brasiliensis***

*(Courtesy of CDC, Dr. Lucille Georg)*



## Aspergillosis

- *A. flavus*, *A. fumigatus*, *A. niger*; ubiquitous in nature (soil, decaying vegetation, dust, leaves); risk factors include neutropenia, bone marrow transplantation, age
  - **Primary cutaneous aspergillosis** presents with local inoculation in weakened host; presents as erythematous macules → necrotic papules, hemorrhagic bullae, ulcers; typical portals of entry include IV catheters, burns, trauma, and surgical wounds; risk of dissemination significant with immunosuppression; of note, blood vessel involvement includes thrombosis, inflammation, and necrosis (*A. flavus* most common primary cutaneous pathogen)
  - Other presentations: pulmonary disease and disseminated disease with hematogenous spread
- Histology: dichotomous branching (equal division) at 45–60°, often involving blood vessels
- Colony: *A. flavus* – yellow to green culture; *A. fumigatus* (most common species) – dark green to gray culture; *A. niger* – white woolly colony turns black with age
- Treatment: amphotericin B, voriconazole, itraconazole

## Zygomycosis (Mucormycosis) (Figures 4.33B–D and 4.34A)

- *Absidia* spp., *Rhizopus* spp., *Mucor* spp. (most common); ubiquitous in nature (soil, fruits, decaying vegetation); risk factors include neutropenia, diabetes mellitus, metabolic acidosis, severe burns, immunosuppression
- Transmission typically via inhalation
  - **Rhinocerebral infection**: typically seen in diabetic patients with nasal or sinus infection under poor control → dissemination or rapid contiguous spread causing indurated necrotic plaque, facial edema, orbital cellulitis, bloody nasal discharge, and cavernous sinus thrombosis
  - **Local cutaneous**: typically secondary infection of a burn, less common catheter-associated infections
- Histology: large ribbon-like hyphae with 90° branching (wider than *Aspergillus*), ring-shaped on cross section, tend to invade blood vessels and form thrombi
- Culture: rapid cotton candy-like growth
- Treatment: amphotericin B and debridement

## Candidiasis

- *Candida* spp.

<i>C. albicans</i>	Most common species
<i>C. glabrata</i>	Fungemia in compromised patients, fluconazole-resistant
<i>C. parapsilosis</i>	Chronic paronychia, endocarditis in IV drug users
<i>C. tropicalis</i>	Frequent dissemination to skin
<i>C. dubliniensis</i>	Oropharyngeal candidiasis in HIV
<i>C. krusei</i>	Endocarditis in IV drug users

- Common opportunistic infection
- Varying presentations in immunocompromised patients: candidal folliculitis, candidal esophagitis, neonatal candidiasis, and candidemia
- Cutaneous findings for candidemia: tiny pink macules and papules → evolve into pustules → papulonecrotic eschars and purpura



**Figure 4.33**

**A:** *Cryptococcus neoformans*  
(Courtesy of Doctor Fungus,  
[www.doctorfungus.org](http://www.doctorfungus.org))

**B:** Mucormycosis  
(Courtesy of Dr. Paul Getz)

**C:** *Mucor* spp.\*

**D:** *Rhizopus* spp.\*

\*Courtesy of Sandra Arduin, Michigan  
Department of Community Health



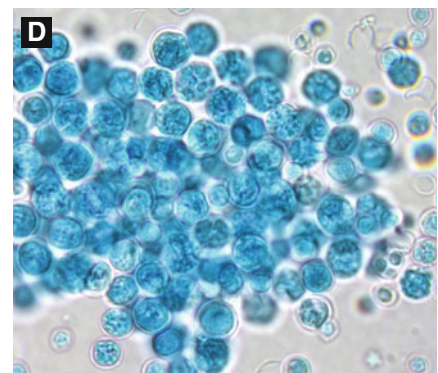
- Histology: pseudohyphae and budding yeast
- Treatment: amphotericin B, ketoconazole, fluconazole, itraconazole, caspofungin
- Of note, cycloheximide partially inhibits *C. tropicalis* and strongly inhibits *C. parapsilosis*

### Rhinosporidiosis (Figure 4.34B, C)

- *Rhinosporidium seeberi*, found mainly in India, Sri Lanka, and Africa; long thought to be fungus but later found to be aquatic protozoan
- Presents after local traumatic inoculation as painless papules involving mainly nasal mucosa → hyperplastic red friable (raspberry-like) polyps
- Histology: characteristic giant sporangia (up to 500  $\mu\text{m}$ ) with thousands of endospores; spherules stain with mucicarmine
- Culture: unable to culture
- Treatment: surgical excision

### Protothecosis (Figure 4.34D)

- *Prototheca wickerhamii*, an achlorophyllic algae found in stagnant aqueous sources (lakes, stream, even tap water)
- Endemic to Southeast Asia
- Presents after traumatic inoculation as solitary cutaneous plaque or nodule typically involving an extremity, may evolve to umbilicated papules in HIV patients; may also present as olecranon bursitis; immunocompetent patients with limited disease but an immunocompromised person may have widespread disease, including algemia
- Histology: morula formation (daughter cells within a theca resembling a soccer ball), 6–10  $\mu\text{m}$  either outside or within macrophage, best seen with GMS or PAS; inhibited by cycloheximide
- Treatment: excision or tetracycline with amphotericin B



**Figure 4.34**

**A: Mucormycosis**

(Courtesy of Dr. Paul Getz)

**B: Rhinosporidiosis\***

**C: Rhinosporidiosis\***

\*Reproduced with permission from:

Kumari R, Laxmisha C, Thappa, DM.

Disseminated cutaneous rhinosporidiosis.

Dermatol Online J. Mar 2005;11 (1):19

**D: Protothecosis**

(Courtesy of Sandra Arduin, Michigan

Department of Community Health)

**Phaeohyphomycosis (Figure 4.35A)**

- Group of dematiaceous fungi: *Alternaria* spp., *Curvularia* spp., *Exophiala* spp., *Bipolaris* spp.
- Found in soil, plants, air, and organic debris
- Local inoculation can produce primary cutaneous infection or may see secondary infection of burns; dissemination only in immunocompromised patients
- Histology: fungi stain best with Fontana-Masson

*Alternaria*: conidia resemble “hand grenades” in chains

**Hyalohyphomycosis (Figure 4.35B)**

- Nondematiaceous hyaline fungi: *Penicillium* spp., *Acremonium* spp., *Fusarium* spp., and *Scopulariopsis* spp.
- Scopulariopsis typically causes nail infections
- Fusarium typically presents in compromised hosts as hemorrhagic and necrotic disseminated skin lesions; fungal keratitis; most common fungal infection in burn victims
- Banana-shaped macroconidia

**Penicilliosis (Figure 4.35C)**

- *Penicillium marneffei*
- Carried by healthy bamboo rats
- Presents with acneiform papules resembling molluscum contagiosum (seen especially in AIDS patients)
- Histology: suppurative granulomatous inflammation with intracellular and extracellular yeast

Following infections may resemble molluscum-like lesions: coccidioidomycosis, cryptococcosis, histoplasmosis, penicilliosis

Organisms found within histiocytes: histoplasmosis, granuloma inguinale, leishmaniasis, penicilliosis (His GIrL Penelope)



**Figure 4.35**

**A: *Alternaria* spp.\***

**B: *Fusarium* spp.\***

**C: *Penicillium* spp.\***

\*Courtesy of Sandra Arduin, Michigan Department of Community Health

**Table 4-15 Microscopic Appearance of Select Fungi and Protozoa**

Organism	Description	Size (μm)
<i>Histoplasma capsulatum</i>	Round yeast with surrounding thin, clear halo; distributed evenly within cytoplasm of histiocyte	2–4
<i>Leishmania</i> spp.	Small, grouped intracellular organisms with rod-shaped kinetoplast, no halo	2–4
<i>Apergillus</i> spp.	Septate hyphae with 45° branching, often in blood vessels	2–4
<i>Penicillium marneffei</i>	Oval to round yeast, may be intracellular or extracellular	3–5
<i>Sporothrix schenckii</i>	Round to cigar-shaped yeast, difficult to find	3–8
<i>Prototheca</i> spp.	Spherule with morula formation with numerous septations (resembles soccer ball)	3–11
<i>Blastomyces dermatitidis</i>	Thick-walled spores, characteristic broad-based budding	8–15
<i>Cryptococcus neoformans</i>	Budding yeast with prominent mucinous capsule (does not stain with H&E)	5–20
<i>Coccidioides immitis</i>	Double contoured spheres with endospores	10–80
<i>Mucor</i> spp.	Broad hyphae with 90° branching	10–25
<i>Paracoccidioides brasiliensis</i>	Characteristic buds resembling mariner's wheel	5–60
<i>Rhinosporidium seeberi</i>	Spherule with endospores (6–10 μm)	250–500

#### 4.4 PROTOZOA AND WORMS

##### **Leishmaniasis** (Figures 4.36 and 4.37)

- *Leishmania* spp., intracellular parasite with >17 species
- Transmitted by sandfly (*Lutzomyia* and *Phlebotomus*) and endemic in South America, Africa, Asia, and Mediterranean countries
- Infection with *Leishmania* species classified as either **Old World** (Africa, Asia, Middle East, Mediterranean) or **New World** (Central/South America, Texas)
- Three clinical forms:
  - **Cutaneous:** small red papule or papules → ulcerate with raised edges → spontaneously heals with scarring; lesions may be wet or dry; *L. major*, *L. mexicana*, *L. braziliensis*
  - **Mucocutaneous:** cutaneous ulcer at inoculation site which heals → mutilating mucosal infection with perforation of nasal septum; *L. braziliensis*, *L. aethiopica*
  - **Visceral:** recurrent fever, hepatosplenomegaly, hyperpigmented patches (“black fever”), diarrhea, death within 2 years if untreated
- Diagnosis: culture unreliable; standard culture medium is Novy-McNeal-Nicolle; PCR sensitive diagnostic test
- Treatment:
  - Cutaneous or mucocutaneous: pentavalent antimonial such as sodium stibogluconate or meglumine antimonite
  - Visceral leishmaniasis: amphotericin B

Of note, pentavalent antimony causes **QT prolongation**, flattened T wave, and/or arrhythmia



**Figure 4.36**  
**Cutaneous leishmaniasis**  
 (Courtesy of Dr. Shyam B. Verma,  
 Vadodara, India)

<b>Cutaneous leishmaniasis</b>	<u>Old World</u> (vector <i>Phlebotomus</i> ): <i>L. major</i> <i>L. donovani</i> <i>L. infantum</i> <i>L. tropica</i> <i>L. aethiopica</i> <i>L. chagasi</i>	<u>New World</u> (vector <i>Lutzomyia</i> ): <i>L. mexicana</i> , <i>L. amazonensis</i> , <i>L. braziliensis</i> , <i>L. peruviana</i>
<b>Mucocutaneous leishmaniasis</b>	<u>Old World</u> (vector <i>Phlebotomus</i> ): <i>L. aethiopica</i>	<u>New World</u> (vector <i>Lutzomyia</i> ) <b><i>L. braziliensis</i></b> , <i>L. peruviana</i>
<b>Visceral (Kala-azar)</b>	<i>L. donovani</i> , <i>L. infantum</i> ,	<i>L. chagasi</i>



**Figure 4.37**  
**Cutaneous leishmaniasis**  
(Courtesy of Dr. Shyam B. Verma,  
Vadodara, India)

**Table 4-16 Select Protozoal Infections**

Disease	Organism/Vector	Clinical Findings	Treatment
<b>Amebiasis</b>	<i>Entamoeba histolytica</i>	Mainly GI symptoms (bloody diarrhea)  Rare skin findings: cysts, nodules, or ulcers with heaped-up borders and erythematous halo	Oral metronidazole
<b>American Trypanosomiasis</b> (Chagas Disease)	<i>Trypanosoma cruzi</i> (Central/South America)  <u>Vector: reduviid bug</u> ( <i>Triatoma spp.</i> )	Erythema and edema at site of inoculation, regional lymphadenopathy  <b>Romaña's sign:</b> eyelid edema and conjunctivitis  <u>Chronic phase:</u> cardiac and GI abnormalities (arrhythmia, <b>heart block</b> , <b>megacolon</b> , megasophagus); infection mainly in children	Nifurtimox or benznidazole
<b>African Trypanosomiasis</b> (Sleeping Sickness)	<i>T. brucei gambiense</i> <i>T. brucei rhodesiense</i>  <u>Vector: tsetse fly</u> ( <i>Glossina spp.</i> )	<u>First stage:</u> indurated chancre at site of inoculation → heals spontaneously; subsequent fever spikes correlating with annular erythematous patches  <b>Winterbottom's sign:</b> posterior cervical lymphadenopathy  <u>Second stage:</u> daytime <b>somnolence</b> (neurologic phase)	Suramin or pentamidine
<b>Toxoplasmosis</b>	<i>Toxoplasma gondii</i>  <u>Vector:</u> contact with cat feces or ingestion of improperly cooked pork	Acute infection typically asymptomatic in competent hosts (± flu-like symptoms) Immunocompromised: <b>CNS toxoplasmosis</b> , pneumonitis, chorioretinitis	Sulfadiazine with pyrimethamine



Table 4-17 Select Helminth Infections

Disease	Organism/Vector	Clinical Findings	Treatment
<b>Cutaneous larva migrans</b>	<u><i>Ancylostoma braziliense</i></u>  Vector: penetration of skin by larvae	Erythematous, serpiginous “tract” with ↑↑ pruritus; typically occurs after walking barefoot in area contaminated by animal feces (eggs in animal feces → passed to soil and larvae hatch)	Topical thiabendazole, oral ivermectin or albendazole
<b>Loiasis</b> Calabar swelling	<u><i>Loa loa</i></u>  Vector: <b>deer or mango fly</b> ( <i>Chrysops</i> , family Tabanidae)	<b>Calabar swelling:</b> subcutaneous edema containing female worm, ± conjunctivitis (adult worm migrating across conjunctiva)	Diethylcarbamazine
<b>Filariasis</b> Elephantiasis	<u><i>Wuchereria bancrofti</i></u>  Vector: mosquitoes ( <i>Aedes</i> , <i>Culex</i> )	<u>Acute:</u> recurrent lymphangitis and fever <u>Chronic:</u> lymphedema, elephantiasis (most commonly involving genitalia and lower leg)	Diethylcarbamazine
<b>Dracunculiasis</b> Guinea worm disease	<u><i>Dracunculus medinensis</i></u>  Vector: infected water crustaceans ( <i>Cyclops</i> )	Ingestion of infected water fleas → wheezing, pruritus, urticaria → worm migrates from GI tract to skin (usually lower leg) where bulla forms and later erupts to release worm and larvae	Thiabendazole or niridazole
<b>Onchocerciasis</b> River blindness	<u><i>Onchocerca volvulus</i></u>  Vector: <b>black fly</b> ( <i>Simulium</i> spp.)	Varying presentations including subcutaneous nodules containing worms, dermatitis, depigmentation on lower legs, and vision loss  <b>Mazzotti reaction:</b> severe reaction with urticaria and systemic signs associated with diethylcarbamazine	Ivermectin or diethylcarbamazine
<b>Schistosomiasis</b> (visceral) Bilharziasis	<u><i>Schistosoma mansoni</i></u> , <u><i>S. haematobium</i></u> , <u><i>S. japonicum</i></u>  Vector: water infected with worm eggs/feces	<u>Acute</u> (Katayama fever): severe urticarial eruption which serum sickness-like symptoms (fever, headache, myalgias, arthralgias)  <u>Chronic:</u> involvement of liver, lungs, bladder, or CNS, ± painless verrucous nodules at sites of ectopic deposition of eggs	Praziquantel
<b>Cercarial dermatitis</b> Swimmer’s itch	<u><i>Trichobilharzia</i> spp.</u> (Avian schistosome)  Vector: water infected with worm eggs/feces	Larvae from infected waters penetrate skin → larvae die immediately but cause short-term immune reaction with pruritic erythematous macules and papules <u>in exposed areas</u> (the species causing this eruption is less pathogenic than in schistosomiasis and cannot enter bloodstream or deeper tissue)	Oral antihistamine and topical antipruritics  Of note, seabather’s eruption on <u>covered</u> areas (due to larvae of thimble jellyfish)
<b>Strongyloides</b> Racing larva Larva currens	<u><i>Strongyloides stercoralis</i></u>  Vector: direct contact with soil contaminated with larvae	Initially see rapidly moving form of larva migrans (5–10 cm/h) → migrates to lungs, ascends, and then is swallowed entering GI tract → larvae excreted via feces, but can cause autoinfection by penetrating perianal skin → intensely pruritic perianal rash with radiating urticarial bands	Albendazole, thiabendazole, or ivermectin

## 4.5 INFESTATIONS

### Scabies (Figure 4.38A)

Unlike adults, infants with scalp/face involvement

- Female itch mite, *Sarcoptes scabiei* var. *hominis*
- Presents with intense pruritus (worse at night) with symmetric papules, vesicles, or indurated nodules typically involving interdigital web spaces, volar wrists, axillae, postauricular areas, ankles, waist, buttocks, waistband area, and genital area; ± visible burrows: gray-white thread-like lesions over finger web spaces
- Diagnosis: mineral oil scraping from burrow
- Treatment with topical scabicide, but pruritus can persist 2–4 weeks after treatment (post-scabietic pruritus)

### Pediculosis Pubis (Pubic Lice) (Figure 4.42A)

- *Phthirus pubis*, crab louse; wider and shorter body than the body louse, resembling miniature crabs
- Presents with itching of pubic area, may be erythema around hair follicles, excoriations, secondary bacterial infection, ± maculae caerulea: slate gray to blue macules
- Treatment same as head lice

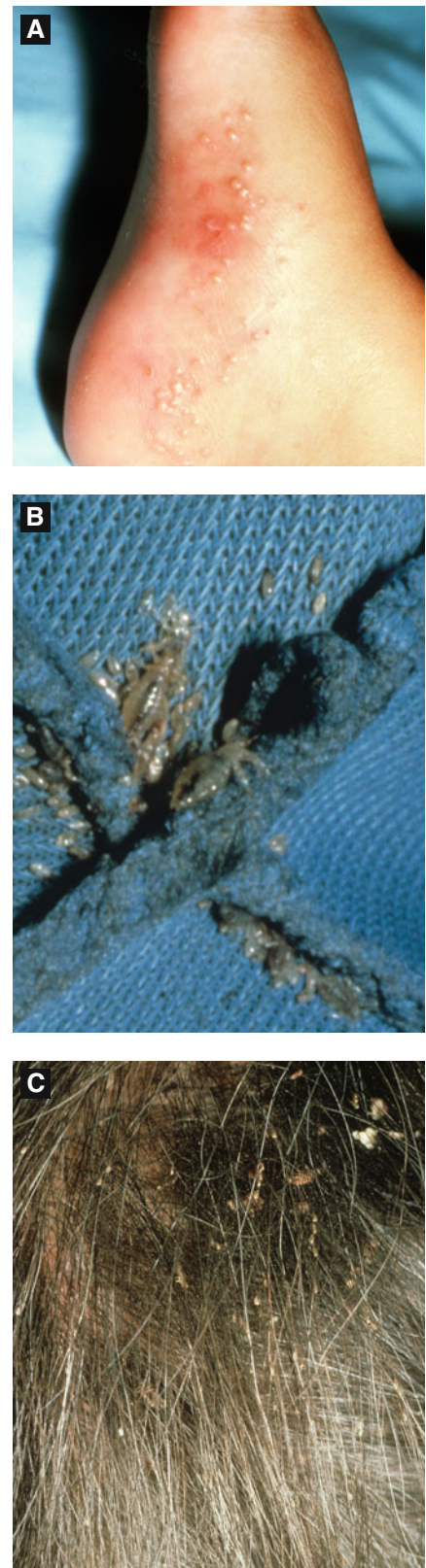
### Pediculosis Corporis (Body Lice) (Figures 4.38B, 4.42B)

- Due to *Pediculus humanus corporis*; infestation of humans and clothing
- Typically infects homeless people; live and lay eggs in clothing (not on people)
- Transmitted by epidemic typhus, trench fever, relapsing fever

### Pediculosis Capitis (Head Lice) (Figure 4.38C)

- Due to *Pediculus humanus capitis*, a bloodsucking, wingless insect
- Feeds every 4–6 h; female lays 5–10 eggs/day close to scalp, cemented to hair
- Presents as scalp pruritus with nits commonly found behind ears and at nape of neck
- Treatment: two applications 1 week apart of pediculicide
  - Malathion: organophosphate, flammable
  - Lindane: organochloride, not first line, neurologic toxicity (seizures, confusion, etc.)
  - Permethrin: synthetic pyrethroid, resistance high
  - Pyrethrin: naturally occurring pyrethroid extract, resistance high

Pyrethrins: derived from chrysanthemum flower (so contraindication if allergic to ragweed or chrysanthemums)



**Figure 4.38**

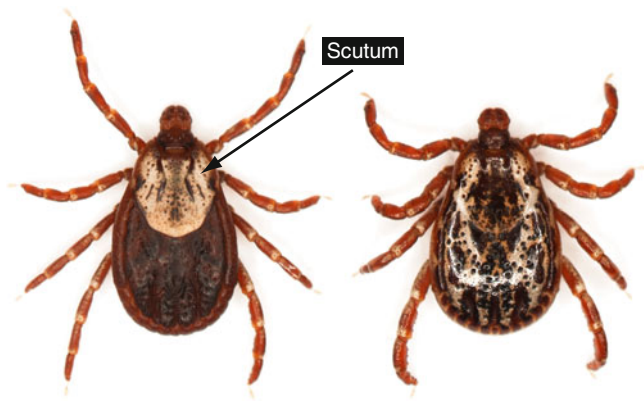


**A: Scabies\***

**B: Body lice in clothing\***

**C: Pediculosis capitis\***

\*Courtesy of Dr. Paul Getz

Table 4-18 Select Tick Diseases

Tick	Disease	Appearance of Tick	Female	Male
<b><i>Dermacentor variabilis</i></b> (American dog tick)  <b><i>Dermacentor andersonii</i></b> (Wood tick)	Rocky Mountain Spotted Fever (RMSF)	<u><i>Female</i></u> : reddish-brown with whitish markings on <b>upper body</b> (scutum)  <u><i>Male</i></u> : whitish markings on <b>entire back</b>		
<b><i>Amblyomma americanum</i></b> (Lone star tick)	Ehrlichiosis Lyme Disease RMSF	<u><i>Female</i></u> : characteristic <b>dorsal white spot</b>  <u><i>Male</i></u> : scattered spots/streaks around <b>perimeter of body</b>		
<b><i>Ixodes scapularis</i></b> (formerly Dammini) (Black legged or deer tick)  <b><i>Ixodes pacificus</i></b> (Western black legged)	Lyme Disease Babesiosis Ehrlichiosis (human granulocytic)	<u><i>Female</i></u> : reddish body, dark brown shield (scutum)  <u><i>Male</i></u> : smaller and completely dark brown		
Tick images courtesy of Entomology & Plant Pathology, Oklahoma State University				

**Table 4-19 Select Spiders (Figures 4.39A–F and 4.40A–B)**

Common name	Scientific Name	Appearance/Toxin	Clinical Findings/Treatment
<b>Black widow spider</b>	<i>Lactrodectus mactans</i>	Black with round abdomen; red <b>hourglass-shaped marking</b> on ventral surface  <u>Toxin</u> : <b><math>\alpha</math>-latrotoxin</b> (depolarizes neuron)	Acute edema and pain at site of bite, systemic symptoms resembling acute <b>surgical abdomen</b>  <u>Treatment</u> : antivenin, benzodiazepine, IV calcium gluconate
<b>Brown recluse spider</b>	<i>Loxosceles reclusa</i>	Light brown with small body and long, delicate legs  <u>Toxin</u> : <b>sphingomyelinase D</b> (phospholipase)	Erythema at site of bite → bulla → necrosis; systemic symptoms associated with disseminated intravascular coagulation  <u>Treatment</u> : ice, elevation, ± dapsone
<b>Hobo spider</b> Funnel web spider	<i>Tegenaria agrestis</i>	Tan to brown hairy spider with <b>herringbone striped pattern</b> on abdomen  <u>Toxin</u> : causes local necrosis and affects CNS	Painless bite, but can lead to <b>necrotic eschar</b> , ± visual changes, weakness, malaise  <u>Treatment</u> : supportive
<b>Wolf spider</b>	<i>Hogna</i> spp.	Brown to gray spider with <b>peach-colored stripe</b> down cephalothorax; eyes arranged in 3 rows, bottom row with <b>four small eyes</b>  <u>Toxin</u> : <b>histamine</b>	Painful bites → ± lymphangitis or eschar  <u>Treatment</u> : supportive
<b>Green lynx spider</b>	<i>Peucetia viridans</i>	<b>Bright green with red spots</b> , black spines on legs	Painful bite with tenderness, pruritus (usually no necrosis)  <u>Treatment</u> : supportive
<b>Sac spider</b>	<i>Cheiracanthium</i> spp.	Beige or pale yellow, no distinguishing markings  <u>Toxin</u> : lipase	Painful bite  <u>Treatment</u> : supportive
<b>Jumping spider</b>	<i>Phidippus</i> spp.	Dark body hairs, variable white pattern, unique eye arrangement with largest two eyes in <b>middle front row</b>  <u>Toxin</u> : <b>hyaluronidase</b>	Painful bite  <u>Treatment</u> : supportive
<b>Tarantula</b>	<i>Theraphosidae</i> spp.	Large hairy spiders  <u>Toxin</u> : <b>urticating hairs</b> thrown at skin and eyes – penetrate epidermis	Pruritus with wheal and flare reaction at site of hair penetration; <b>ophthalmia nodosa</b> (ocular inflammation with exposure to hairs, can lead to vision loss)  <u>Treatment</u> : supportive



**Table 4-20 Select Arthropods and Other Creatures (Figures 4.41A–F, 4.42C, D and 4.43C, E)**

Common Name	Scientific Name and Virulence Factor	Clinical Presentation	Treatment
<b>Scorpion</b>	<i>Centruroides</i> spp. <u>Virulence</u> : two poison glands empty into stingers	<b>Pain and paresthesias</b> , variable swelling at site of sting, $\pm$ neurologic or cardiopulmonary complications	Remove stinger, local wound care, ice, antihistamines
<b>Myiasis</b>	<i>Dermatobia hominis</i> (botfly larva)	Larva penetrates into skin causing pyogenic furuncle or “furuncular myiasis”	Extract maggot manually or occlude with petrolatum
<b>Centipedes</b> (Class: Chilopoda)	<i>Scolopendra</i> spp. <i>Scutigera</i> spp. <u>Virulence</u> : nocturnal carnivores; inject neurotoxic venom through ducts in jaws	Two hemorrhagic puncture wounds at site of bite (form chevron shape), $\pm$ pain, edema, erythema, profuse bleeding, and associated <b>paresthesias</b>	Symptomatic treatment and systemic antihistamine
<b>Millipedes</b> (Class: Diplopoda)	<u>Virulence</u> : harmless vegetarians (do not bite) may emit toxic substance	Contact dermatitis to noxious chemical with associated burning, blistering, and/or pigmentation, $\pm$ severe inflammation of eyes (if toxin squirted)	Symptomatic treatment with copious lavage to affected site
<b>Snake bites</b>	<u>Crotalidae family</u> : rattlesnake, copperhead, and cottonmouth moccasin <u>Elapidae family</u> : coral snake <u>Virulence</u> : venom (mainly hydrolases)	Rapid onset pain and swelling (within hour of envenomation), hemorrhage, and necrosis common with paired bite marks	Antivenom therapy, tetanus prophylaxis, antibiotic if needed
<b>Bees, wasps, hornets</b>	<u>Virulence</u> : phospholipase (honey bee venom)	Range from mild pain with local edema to exaggerated reactions, $\pm$ generalized urticaria, angioedema, respiratory distress, shock	Remove stinger, ice, symptomatic care
<b>Fire ants</b>	<i>Solenopsis</i> spp. <u>Virulence</u> : hemolytic factor, <b>solenopsins</b> (piperidine alkaloids from venom of red fire ant)	Sterile pustule with erythematous hemorrhagic halo, large urticarial lesions, systemic neurologic symptoms (if multiple bites), $\pm$ anaphylaxis, shock, and death	Symptomatic care
<b>Bed bugs</b>	<i>Cimex lectularius</i> (Small, reddish-brown with oval-shape and banded appearance)	Pruritic macules and papules typically involving exposed skin, often grouped in three (“breakfast, lunch, dinner”); peak occurrence before sunrise	Symptomatic care for skin lesions; eliminate infestation
<b>Blister beetle</b>	<i>Lytta vesicatoria</i> <u>Virulence</u> : <b>cantharidin</b> (blistering agent)	Vesicles or bullae after contact with skin	Symptomatic care
<b>Carpet beetle</b>	<i>Anthrenus</i> spp. <i>Attagenus</i> spp. (Shiny black and oval-shaped)	May cause allergic papulovesicular dermatitis on exposed areas (due to adults or larvae)	Symptomatic care
<b>Sea urchin</b>	<u>Virulence</u> : fragile spines, break easily into the skin	Fragments of spines in skin, may cause synovitis and arthritis if near joints	Remove spines

*Continued on the next page*

**Table 4-20 Select Arthropods and Other Creatures (cont'd)**

Common Name	Scientific Name and Virulence Factor	Clinical Presentation	Treatment
<b>Sea bather's eruption</b>	<i>Linuche unguicalata</i> (thimble jellyfish larvae) <i>Edwardsiella lineate</i> (sea anemone)	Stinging larvae trapped beneath swim-wear → pruritic papules under covered areas ( <b>bathing suit distribution</b> )	Symptomatic
<b>Jellyfish stings</b>	<i>Chironex fleckeri</i> (Pacific box jellyfish) <i>Physalia physalis</i> (Portuguese man of war) <i>Cyanea and Chrysaora</i> (sea nettles)	Sting results in immediate pain, delayed cutaneous reactions, ± shock	
<b>Tungiasis</b>	<i>Tunga penetrans</i>	Flea burrows into upper dermis (resembles abscess with black center or punctum) and discharges eggs from center	
<b>Caterpillars</b>	See Table 4-21 Urticating hairs (setae)	Purely cutaneous reaction ( <u>erucism</u> ) or systemic symptoms without cutaneous findings ( <u>lepidopterism</u> )	Removal of offending hairs (duct tape stripping), topical antipruritics

**Table 4-21 Select Caterpillars (Figure 4.40C–F)**

	Types of Caterpillars (Lepidoptera)	
<b>Puss</b> (Woolly slug)	<i>Megalopyge opercularis</i>	Intense burning pain with <b>hemorrhagic linear track marks</b> (due to parallel rows of stiff hollow spines on dorsum of caterpillar)
<b>Io moth</b>	<i>Automeris io</i>	Nettle-like stinging with papulourticarial eruption, resolves within hours
<b>Saddleback</b>	<i>Acharya stimulea</i>	Immediate stinging with urtication
<b>Browntail moth</b>	<i>E. chrysorrhea</i>	Eczematous or urticarial eruption in exposed areas, typically resolves in 7 days; can develop more serious symptoms (conjunctivitis, rhinitis, bruising)
<b>Gypsy moth</b>	<i>L. dispar</i>	Capable of wind dispersion and urtication: eczematous, pruritic dermatitis with urticaria on exposed areas
<b>White marked tussock moth</b>	<i>Orgyia leucostigma</i>	Papulourticarial eruption after contact

**Table 4-22 Select Vectors (Figures 4.42E–F and 4.43B)**

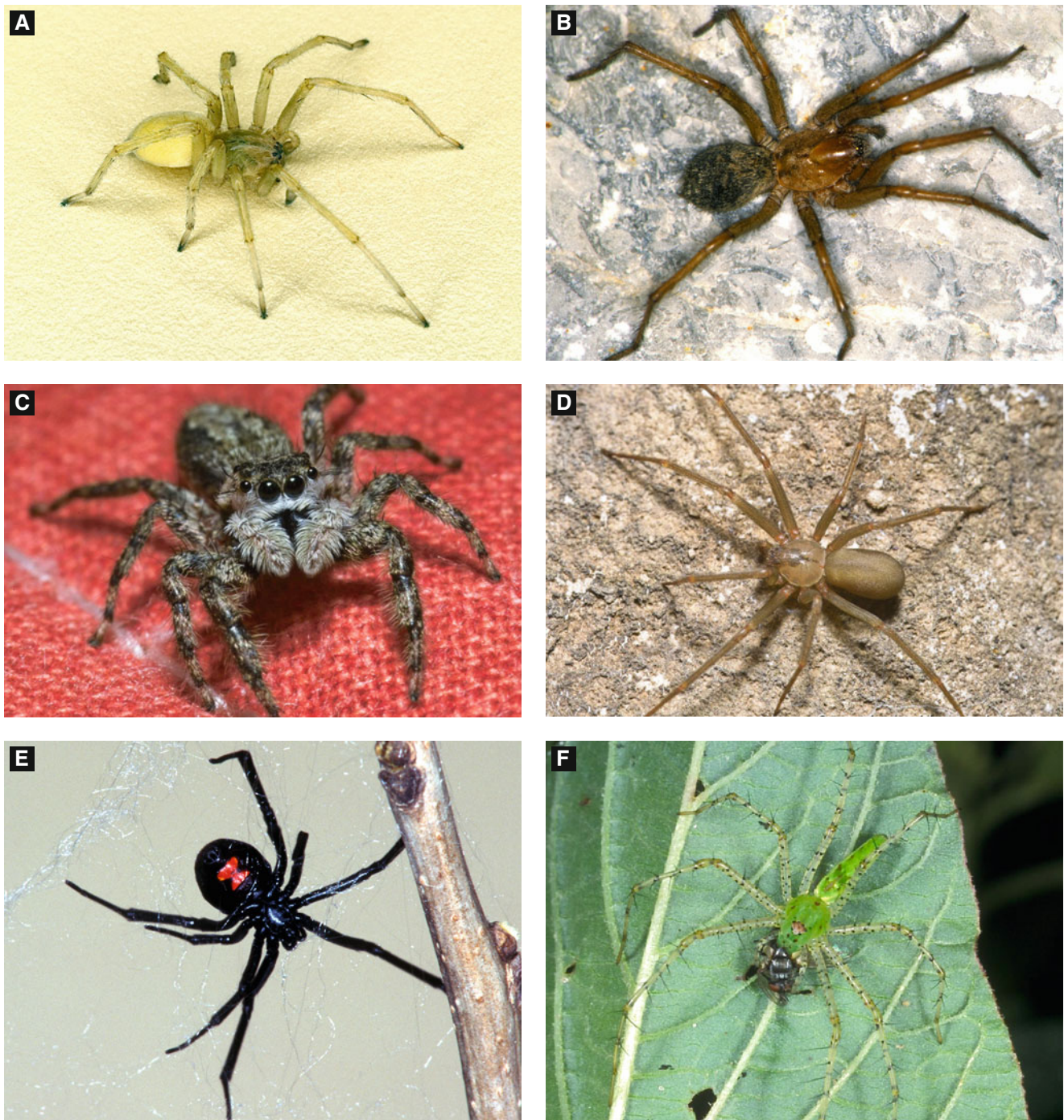
Vector	Disease
<b>Flies</b>	<i>Simulium</i> (black fly) → onchocerciasis <i>Chrysops</i> (deer fly, mango fly) → loiasis, tularemia <i>Tabanus</i> (horse fly) <i>Phlebotomus</i> spp. (sandfly) → leishmaniasis <i>Lutzomyia</i> spp. (sandfly) → leishmaniasis <i>Glossina</i> spp. (tsetse fly) → African trypanosomiasis
<b>Mosquitoes</b>	<i>Anopheles</i> spp. → malaria <i>Aedes</i> spp. → yellow fever, dengue fever
<b>Fleas</b>	<i>Ctenocephalides felix</i> (cat flea) → endemic or murine typhus, cat-scratch disease <i>Xenopsylla cheopis</i> (rat flea) → plague, endemic typhus <i>Pulex irritans</i> (human flea) <i>Ctenocephalides canis</i> (dog flea)
<b>Reduviid bugs</b> <b>Assassin bugs</b> <b>Kissing bugs</b>	Order: Hemiptera; Family: Reduviidae <i>Triatoma</i> spp. (assassin bug or kissing bug) → Chagas disease

**Table 4-23 Select Mites (Figure 4.43A)**

Mite	Common Name	Disease
<i>Acarus siro</i>	Grain mite (found in hay, grain, and house dust)	Baker's itch
<i>Allodermanyssus</i> ( <i>Liponyssoides</i> ) <i>sanguineus</i>	House mouse mite	Rickettsialpox
<i>Cheyletiella</i>		Walking dandruff (cats, dogs, rabbits)
<i>Dermanyssus gallinae</i>	Fowl mite	Equine encephalitis
<i>Dermatophagoides farinae</i>	Dust mite	Allergic reaction
<i>Glyciphagus domesticus</i>	Cheese mite Grocer's mite (found in cheese, grains, hay, mattress)	Grocer's itch
<i>Laelaps</i> , <i>Androlaelaps</i> , <i>Eulaelaps</i>	Rodent mites	Murine typhus, tularemia, spotted fever
<i>Pyemotes ventricosus</i>	Straw itch mite	
<i>Trombicla alfreddugesi</i>	Chigger mite	Bites (group pruritic vesicles/papules on lower legs) – larva attaches to host and drops off after feeding



## 4.6 CREATURES OF SIGNIFICANCE



**Figure 4.39**

**A: Yellow sac spider**

(Courtesy of Jim Kalisch, Department of Entomology, University of Nebraska)

**B: Hobo spider\***

(Courtesy of Jim Kalisch, Department of Entomology, University of Nebraska)

**C: Jumping spider**

(Courtesy of Steve Clark)

**D: Brown recluse spider**

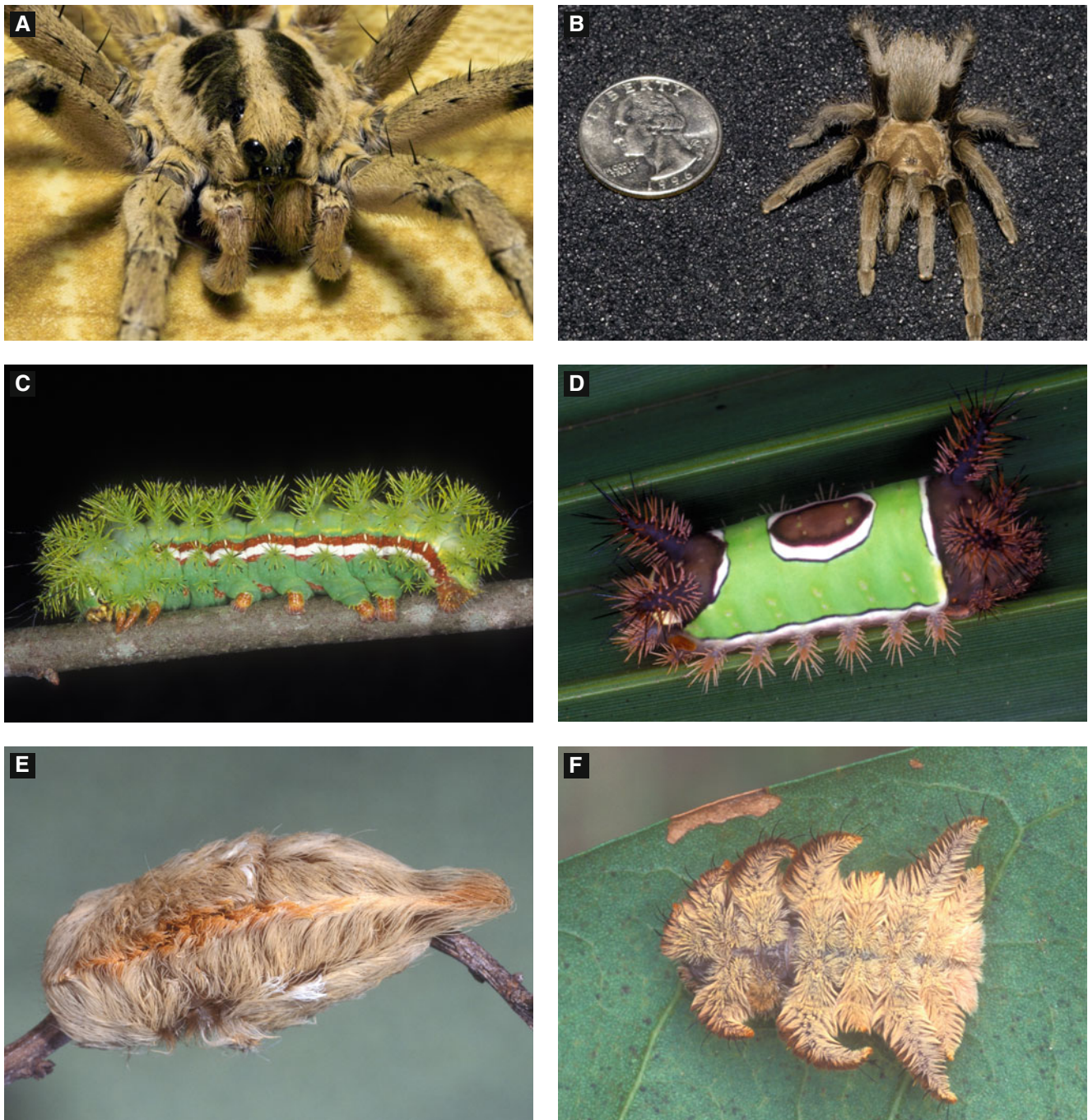
(Courtesy of Steve Clark)

**E: Black widow spider\***

**F: Green lynx spider\***

\*Courtesy of Lyle Buss, Entomology and Nematology Department, University of Florida





**Figure 4.40**

**A: Wolf spider**

*(Courtesy of Steve Clark)*

**B: Tarantula**

*(Courtesy of Steve Clark)*

**C: Io moth\***

**D: Saddleback caterpillar\***

*(Photo taken by James Castner)*

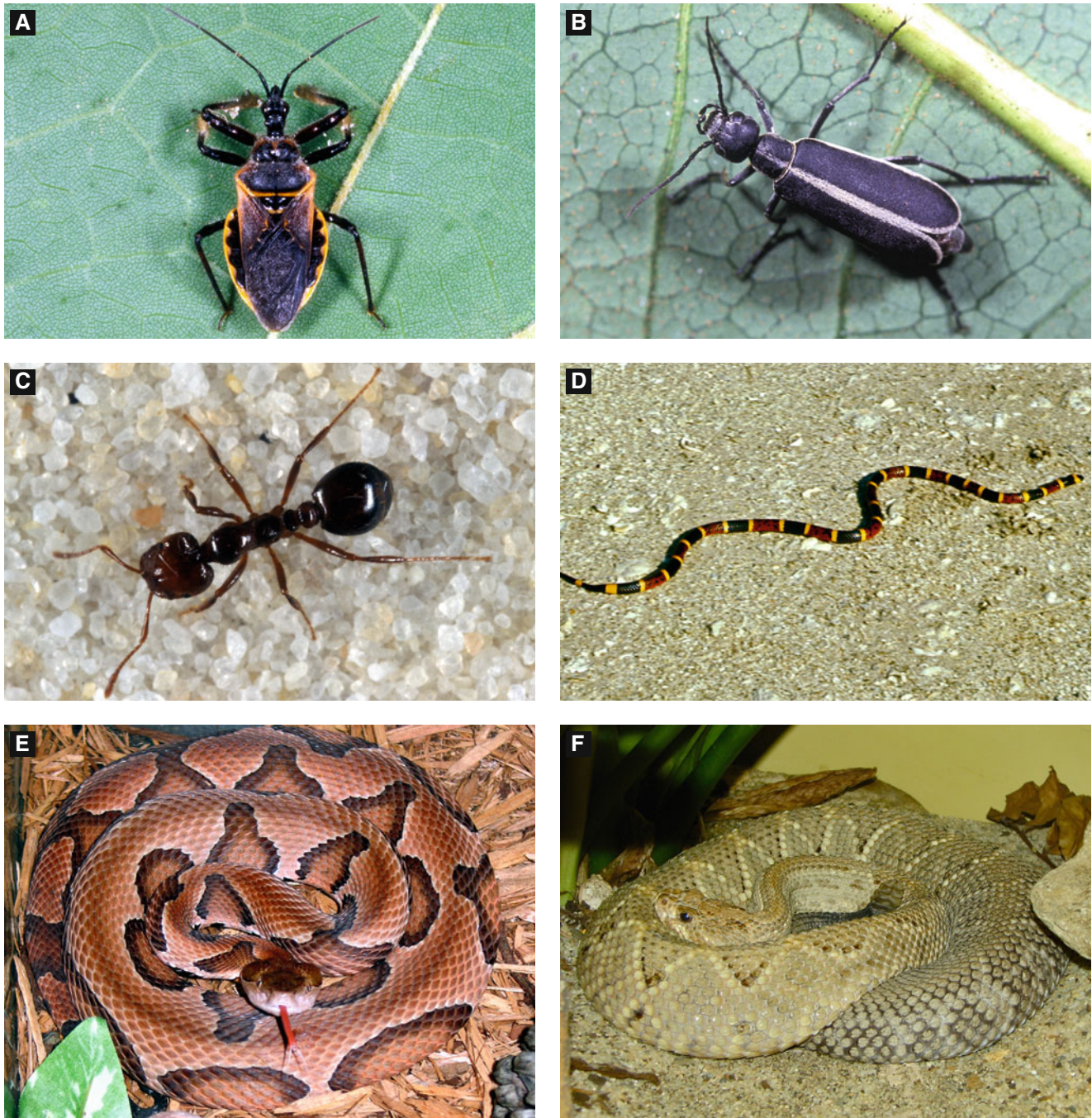
**E: Puss caterpillar\***

*(Photo taken by Paul Choate)*

**F: Hag moth caterpillar\***

*\*Courtesy of Lyle Buss, Entomology and Nematology Department, University of Florida*





**Figure 4.41**

**A: Reduviid bug\***

**B: Blister beetle\***

(Photo taken by James Castner)

**C: Fire ant\***

**D: Coral snake**

(Courtesy of Luther C. Goldman)

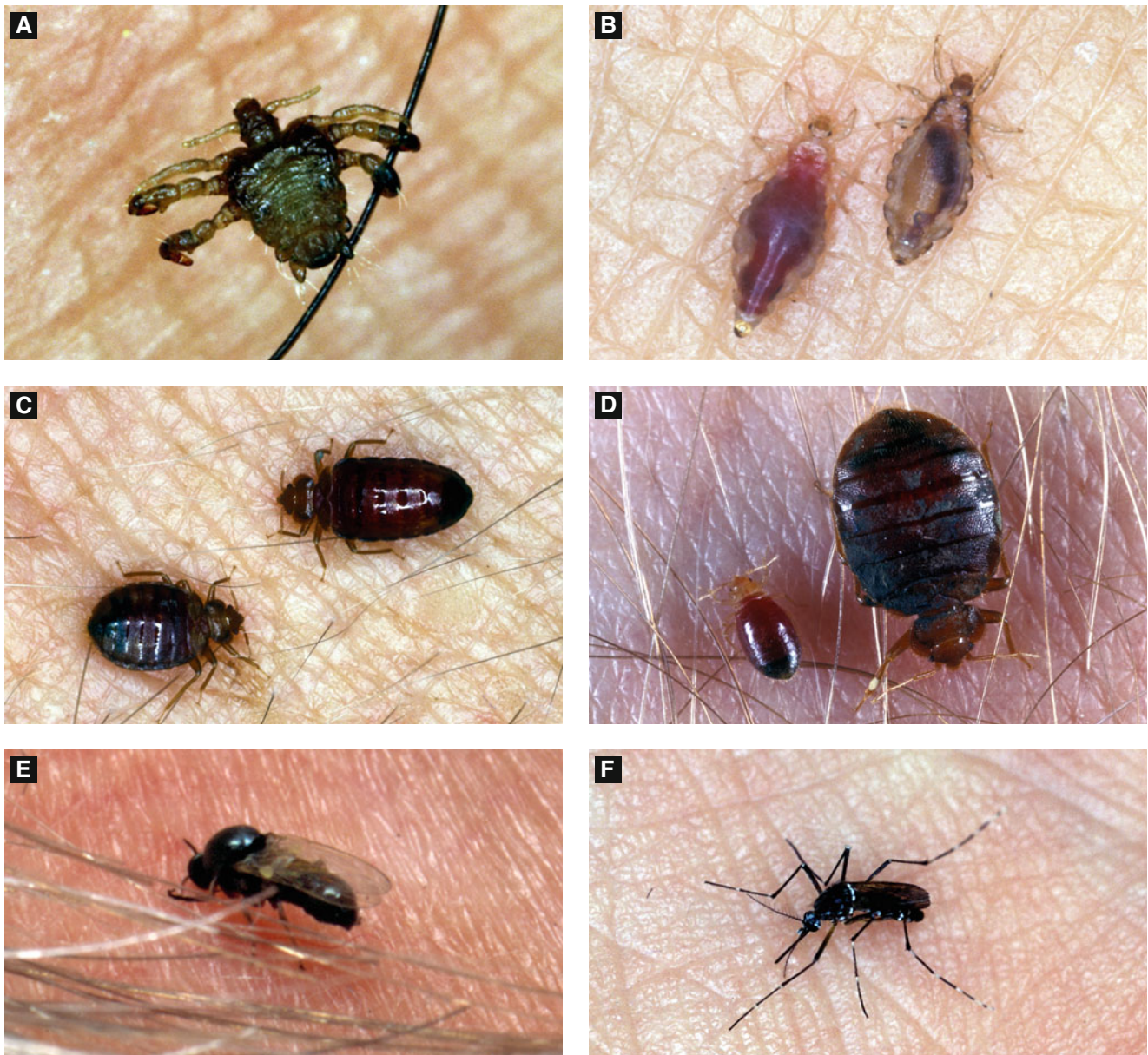
**E: Copperhead snake (Courtesy of CDC)**

**F: Rattlesnake**

(Courtesy of Trisha M. Shears)

\*Courtesy of Lyle Buss, Entomology and Nematology Department,  
University of Florida





**Figure 4.42**

**A: Pubic louse\***

(Photo taken by James Castner)

**B: Body louse\***

(Photo taken by James Castner)

**C: Bed bug\***

(Photo taken by James Castner)

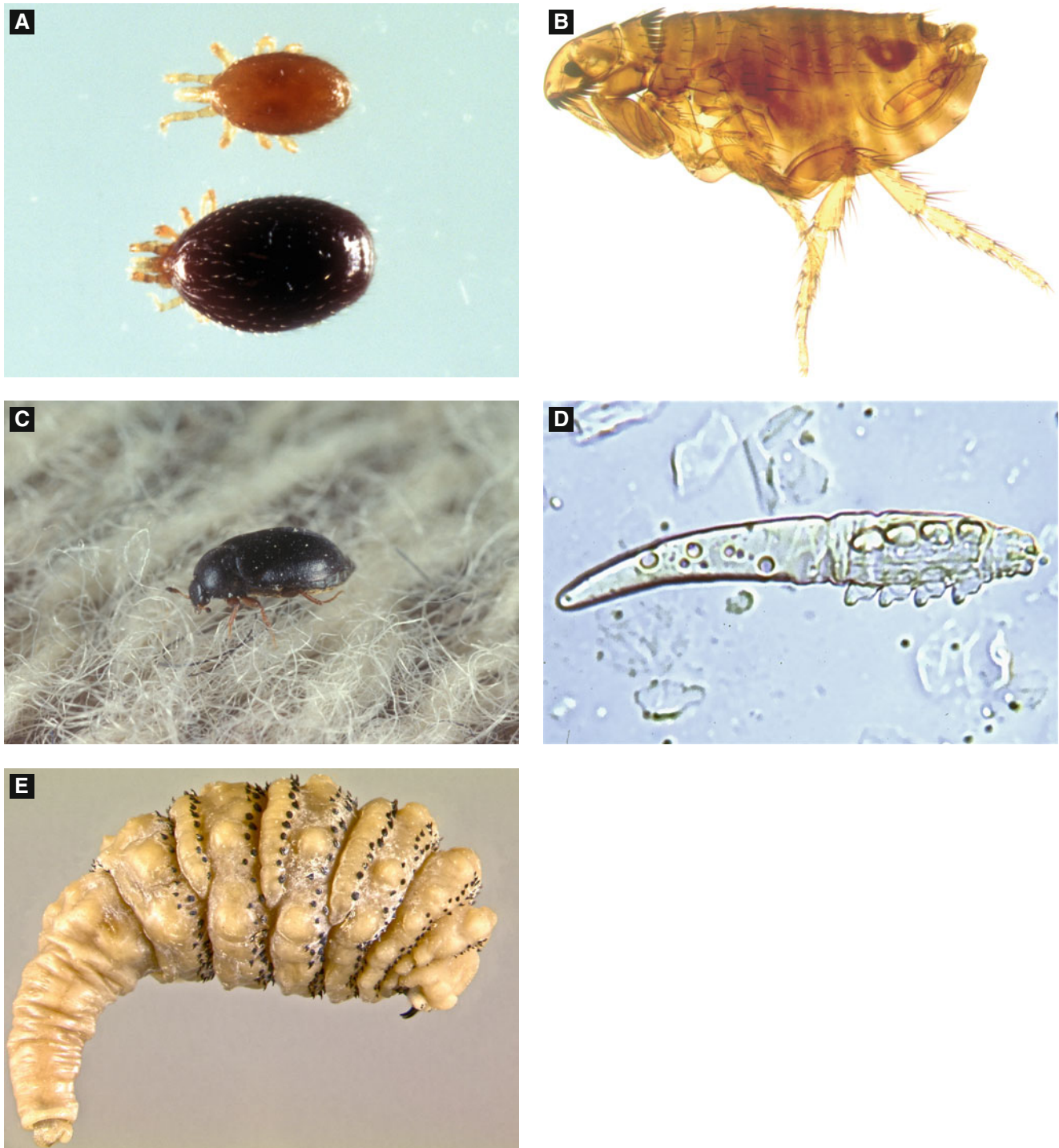
**D: Bed bug\***

**E: Black fly\***  
(Photo taken by Jerry F. Butler)

**F: Yellow fever mosquito\***

(Photo taken by James Castner)

\*Courtesy of Lyle Buss, Entomology and Nematology Department,  
University of Florida



**Figure 4.43**

**A:** Tropical fowl mite\*

**B:** Cat flea\*

**C:** Carpet beetle\*

**D:** *Demodex folliculorum*\*

(Photo taken by Jerry F. Butler)

**E:** Botfly larva (*Dermatobia hominis*)\*

\*Courtesy of Lyle Buss, Entomology and Nematology Department,  
University of Florida



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# 5

## Benign and Malignant Tumors

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## 5.1 BENIGN EPIDERMAL AND DERMAL TUMORS

### **Seborrheic Keratosis (SK)** (Figure 5.1A–C)

- Common benign growth often seen after third decade of life
- Typically light brown to yellow to dark brown papule or plaque with waxy or verrucous appearance and “stuck on” appearance
- Histology: hyperkeratosis, papillomatosis, acanthosis of epidermis, horn pseudocysts, and often increased melanin in basal layer or throughout entire epidermis
- At least five histological variants:
  - **Acanthotic SK:** most frequently seen histologic type; smooth dome-shaped papule with slight hyperkeratosis/papillomatosis but significant acanthosis and many invaginated horn pseudocysts, increased amount of melanin within keratinocytes
  - **Hyperkeratotic SK:** exophytic lesion with significant hyperkeratosis and papillomatosis, only mild acanthosis, fewer horn pseudocysts
  - **Reticulated (adenoid) SK:** interlacing thin strands of basaloid cells and horn pseudocysts
  - **Clonal SK:** intraepidermal well-defined nests of basaloid cells with uniform appearance
  - **Irritated SK:** squamous eddies (whorls of eosinophilic keratinocytes) within epidermis, ± scattered necrotic keratinocytes, lymphoid infiltrate (lichenoid, perivascular or diffuse)
  - **Pigmented SK (melanoacanthoma):** acanthotic, heavily pigmented SK
- Treatment: reassurance, cryotherapy, curettage, shave removal, laser treatment

**Sign of Leser-Trelat:** sudden eruption of SKs typically on trunk and associated with underlying adenocarcinoma (i.e., stomach, colon, etc.)

### **Clear Cell Acanthoma (Degos' Acanthoma)**

- Benign, solitary erythematous papule or plaque most often on the leg
- Histology: sharply demarcated psoriasiform epidermal hyperplasia containing large, pale keratinocytes with + PAS staining (due to glycogen within cells), exocytosis of neutrophils, ± parakeratotic crust



**Figure 5.1**

**A:** Seborrheic keratosis

**B:** Seborrheic keratosis

**C:** Multiple SKs

**Dermatofibroma (DF or Benign Fibrous Histiocytoma)**

(Figure 5.2A, B)

- Common benign fibrohistiocytic tumor often on the leg
- Presents as pigmented or pink firm, dome-shaped papule with central induration, + dimple sign (dimpling of skin with inward compression of lesion)
- Histology: poorly circumscribed nodular proliferation in dermis of spindle-shaped fibroblasts with storiform pattern, hyalinized collagen at periphery of lesion (“keloidal collagen”) with fibroblasts around collagen (“collagen trapping”), epidermal hyperplasia ± flattened (“tabled”) rete ridges, ± basal layer hyperpigmentation
- Variants: atrophic DF, cellular DF, xanthomatous DF, hemosiderotic DF

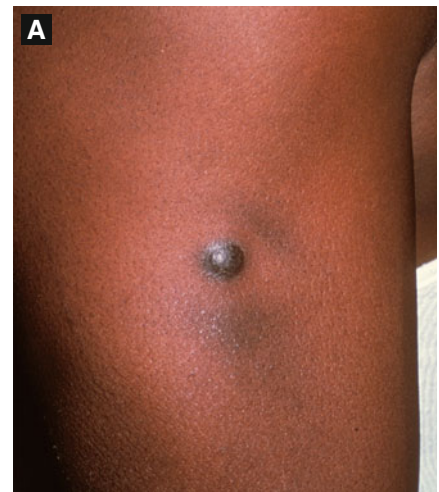
Multiple DFs seen in LE, atopic dermatitis, and immunosuppression

**Giant Cell Tumor of Tendon Sheath**

- Presents as slow-growing, firm skin-colored nodule on finger or toe, fixed to underlying tendon sheath or fascia
- Histology: well-demarcated lobular collection of cells in dermis with fibroblasts and histiocytes, characteristic multinucleated giant cells (osteoclast-like with haphazard nuclei), hemosiderin

**Angiofibroma (Fibrous Papule) (Figure 5.2C)**

- General term for lesions with similar histologic features and includes periungual fibromas, fibrous papules and pearly penile papules
- Presents as skin-colored to red solitary dome-shaped papule most often on nose or central face; pearly penile papules present as dome-shaped small papules circumferentially around corona of glans penis
- Multiple angiofibromas seen in tuberous sclerosis
- Histology: dome-shaped papule with ↑ fibroblasts, collagen oriented concentrically around follicles or perpendicular to epidermis, ↑ dilated blood vessels



**Figure 5.2**  
**A: Dermatofibroma**  
 (Courtesy of Dr. Paul Getz)  
**B: Dermatofibroma**  
**C: Pearly penile papules**



### **Acquired Digital Fibrokeratoma (Acral Fibrokeratoma)** (Figure 5.3A)

- Solitary pink or brown keratotic excrescence on finger with surrounding collarete of elevated skin
- May resemble supernumerary digit
- Histology: massive orthokeratosis and thick, vertically oriented collagen bundles in dermis, blood vessels surrounding collagen bundles

Supernumerary digit (Figure 5.3B, C): see ↑ # of nerves (unlike acquired digital fibrokeratoma)

### **Neurofibroma (NF)**

- Common benign growth; multiple NFs or plexiform NF associated with neurofibromatosis
- Presents typically as solitary, slow-growing skin-colored to pink papule with soft or rubbery feel, ± pedunculated, + “buttonhole sign” (invagination with compression by finger)
- Histology: typically unencapsulated somewhat demarcated nodular proliferation in dermis consisting of spindle cells with wavy nuclei, pale “bubble gum” stroma or fibromyxoid stroma, and mast cells

### **Neuroma**

- Tumor of neural tissue; two types which include traumatic neuroma (amputation neuroma) and palisaded encapsulated neuroma (PEN)
- Often presents as solitary skin-colored to erythematous firm papule, ± associated pain (occurs as site of trauma if traumatic neuroma)
- Histology:
  - **Traumatic neuroma:** well-circumscribed nodule consisting of fascicles of peripheral nerve arranged in a haphazard pattern
  - **PEN:** well-demarcated proliferation of palisading spindle cells with encapsulation and fibrotic stroma

### **Schwannoma (Neurilemmoma)**

- Benign nerve sheath tumor consisting of Schwann cells
- Presents as subcutaneous skin-colored papulonodule often on extremity with occasional tenderness or pain
- Histology: well-circumscribed, encapsulated deep dermal or subcutaneous tumor consisting of two areas (below), mast cells common
  - **Antoni A tissue:** cellular areas consisting of spindle cells with palisaded nuclei arranged in parallel rows with intervening acellular area (Verocay bodies)
  - **Antoni B tissue:** hypocellular myxoid areas

### **Neurothekeoma**

- Pink, red, or brown papulonodule often involving head; can be soft or firm
- Histology: well-demarcated mass in reticular dermis or subcutaneous tissue consisting of myxoid nests or fascicles composed of spindle or epithelioid cells with vesicular nuclei, fascicles divided by fibrous septae



**Figure 5.3**

**A:** Acquired digital fibrokeratoma\*

**B:** Supernumerary digit\*

**C:** Supernumerary digit\*

\* Courtesy of Dr. Paul Getz

**Eccrine Poroma** (Figure 5.4A, B)

- Presents as erythematous papule, plaque or nodule with characteristic “moat” surrounding lesion; often on palm, sole, or scalp
- Histology: well-circumscribed tumor appearing in lower part of epidermis and extending into dermis, cells consist of small cuboidal epithelial (“poroid”) cells which are more pale than normal keratinocytes (may be clear due to glycogen accumulation), small sweat ducts seen within tumor, sharp demarcation between poroid cells and surrounding keratinocytes

**Nodular Hidradenoma (Clear Cell Hidradenoma)**

- Benign adnexal neoplasm presenting as solitary skin-colored nodule with no site predilection
- Histology: well-demarcated nodular proliferation in dermis or subcutaneous tissue consisting of uniform basaloid cells (can have clear cell change), hyalinized collagen in stroma,  $\pm$  sweat ducts within tumor

**Eccrine Spiradenoma**

- Presents as erythematous, blue or gray nodule,  $\pm$  painful
- Histology: sharply delineated basophilic nodule or nodules (“cannon balls” or “blue balls”) in dermis with two types of cells present (small, dark basaloid cells in rosette pattern and large pale cells)

**Cylindroma** (Figure 5.4C)

- Presents as single or multiple firm, rubbery nodules with erythematous to blue color, often on scalp
- Histology: well-demarcated basaloid proliferation in dermis consisting of discrete lobules of cells arranged in “jigsaw” or mosaic pattern, hyalinized cylinders seen surrounding lobules, and hyalinized droplets often admixed with tumor cells
- Multiple cylindromas seen with CYLD mutation either in cylindromatosis or in conjunction with other skin appendage tumors in Brooke–Spiegler syndrome

**Trichilemmoma**

- Neoplasm with differentiation toward follicular outer sheath
- Presents as solitary or multiple smooth-surfaced or verrucoid papules or nodules on face
- Histology: downward lobular growth of epidermis consisting of pale or clear keratinocytes, periphery of lobules with palisading basal keratinocytes and eosinophilic hyaline membrane
- Multiple trichilemmomas seen in Cowden disease

**Figure 5.4****A: Eccrine poroma, scalp\*****B: Eccrine poroma, plantar**

(Courtesy of Dr. Sophie M. Worobec)

**C: Cylindroma\***

\*Courtesy of Dr. Paul Getz



**Inverted Follicular Keratosis** (Figure 5.5A)

- Presents as white, tan, or pink papule often on face (especially cheek or upper lip)
- Histology: endophytic proliferation of pale keratinocytes,  $\pm$  squamous eddies,  $\pm$  horn cysts

**Trichoepithelioma** (Figure 5.5B)

- Benign neoplasm with follicular differentiation
- Presents as skin-colored papule or nodule with predilection for nose, can be solitary or multiple
- Histology: symmetric growth of basaloid tumor islands forming reticulate cords with foci of bulbar differentiation,  $\pm$  horn cysts
- Multiple seen in Brooke–Spiegler syndrome

**Desmoplastic Trichoepithelioma**

- Firm, skin-colored to erythematous annular plaque with central depression typically seen on upper cheek
- Histology: thinner cords of basaloid cells arrayed interstitially among dense collagenous stroma,  $\pm$  horn cysts,  $\pm$  calcium deposits
- Histology resembles sclerosing BCC but benign lesion

**Syringoma** (Figures 5.5C and 5.6A)

- Small papules often clustered over eyelids, less often disseminated over trunk
- Histology: proliferation in superficial dermis consisting of comma-shaped eccrine ducts (resembling tadpoles), fibrotic stroma,  $\pm$  horn cysts  $\pm$  milia

**Hidradenoma Papilliferum**

- Presents as smooth papule or subcutaneous nodule almost always involving vulva
- Histology: circumscribed proliferation in dermis consisting of mazelike glandular spaces lined by tall columnar pale cells and myoepithelial cells, foci of decapitation secretion, no connection to epidermis

**Syringocystadenoma Papilliferum**

- Presents as papule or plaque with papillomatous or crusted surface often on head or neck
- Histology: acanthotic epidermis with cystic invaginations containing numerous villous projections lined by two layers of epithelial cells (columnar and small cuboidal), plasma cells in stroma, decapitation secretion

**Figure 5.5****A: Inverted follicular keratosis\*****B: Trichoepitheliomas\*****C: Syringoma**

\*Courtesy of Dr. Paul Getz

**Granular Cell Tumor**

- Often solitary, skin-colored to brown-red papulonodule often on head/neck (especially tongue)
- Histology: poorly demarcated nodule in dermis consisting of large, pale cells with granular cytoplasm and centrally located nucleus, intracytoplasmic granules called pustulo-ovoid bodies of Milian, may see striated skeletal muscle if lesion on tongue

**Cutaneous Leiomyoma** (Figure 5.6B)

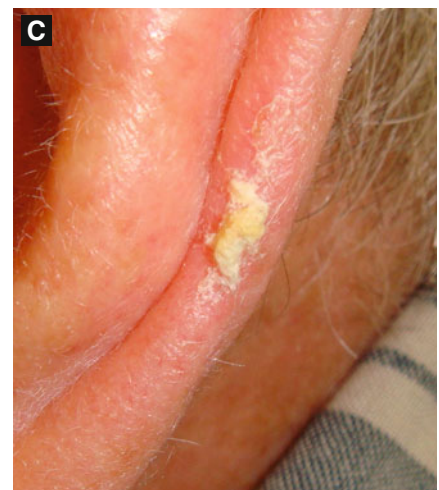
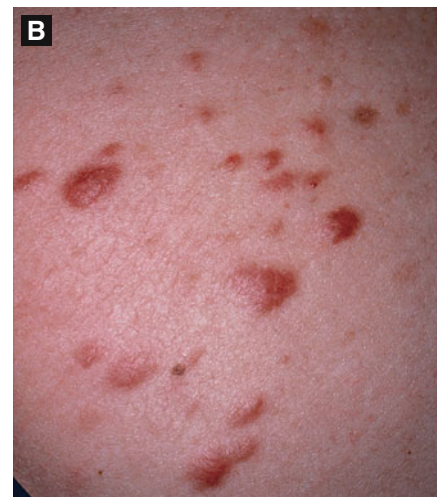
- Presents as reddish brown, pink or skin-colored papules,  $\pm$  painful, may be solitary or multiple; often seen during adolescence or early adulthood
- Histology: neoplasm composed of bland-appearing myocytes with eosinophilic cytoplasm arranged in intersecting fascicles, cells contain elongated nuclei with “cigar-shape” on longitudinal section; cross-section shows round nuclei and vacuoles
- **Reed’s syndrome** (multiple cutaneous and uterine leiomyomatosis syndrome): multiple cutaneous and uterine leiomyomas,  $\uparrow$  risk of renal malignancy, mutation in fumarate hydratase

**Angiolipoma**

- Tumor consisting of mature lipocytes and blood vessels
- Presents as soft subcutaneous nodules often on forearms of young adults, often with pain
- Histology: well-circumscribed neoplasm of mature adipose tissue with a variable number of small vessels,  $\pm$  fibrin thrombi within vessels,  $\pm$  mast cells

**5.2 PREMALIGNANT AND MALIGNANT TUMORS****Actinic Keratosis** (Figure 5.6C)

- Common premalignant lesion in sun-exposed areas with potential to transform into squamous cell carcinoma (percentage varies)
- Presents as erythematous macule or thin papule with adherent scale in sun-exposed areas (easier to identify with palpation)
- Histology: focal parakeratosis, atypical keratinocytes with nuclear pleomorphism and crowding (partial-thickness dysplasia), disordered maturation, prominent solar elastosis in dermis
- Variants: pigmented AK, acantholytic AK, bowenoid AK, lichenoid AK, atrophic AK, hypertrophic AK, actinic cheilitis (confluence of AKs typically on lower lip), cutaneous horn (conical excrescence)
- Treatment: cryotherapy, topical 5-fluorouracil (5-FU), topical imiquimod, chemical peels, photodynamic therapy (PDT)

**Figure 5.6****A: Syringomas**

(Courtesy of Dr. Paul Getz)

**B: Cutaneous leiomyomas**(Reprint from Bologna JL, Rapini R, Jorizzo JL. *Dermatology*. 2nd ed. St. Louis, MO: Mosby; 2008)**C: Actinic keratosis**



**Bowen's Disease (SCCIS)** (Figure 5.7A)

- Squamous cell carcinoma *in situ* commonly presenting as a well-demarcated erythematous patch or plaque often in sun-exposed sites or mucous membrane; can also appear in sun-protected sites presenting as a pigmented plaque (often in dark-skinned patients); predilection for lower limbs in women and ear/scalp in men
- Histology: full-thickness dysplasia of squamous epithelium with disorderly maturation of epidermis (loss of polarity, cytologic atypia, overall “wind-blown” appearance), overlying parakeratosis, loss of granular layer, possible stromal inflammation
- Variants include atrophic, verrucous, pigmented and pagetoid variants, erythroplasia of Queyrat (on glans penis)
- Treatment: surgical excision, electrodesiccation and curettage, photodynamic therapy (PDT), cryosurgery, topical imiquimod

**Squamous Cell Carcinoma (SCC)** (Figure 5.7B, C)

- Second most common type of skin cancer; often presents as erythematous keratotic papule, plaque or nodule typically in sun-exposed sites
- High risk for metastasis: SCC on lip or ear (10–20%), recurrent SCCs (up to 30%), SCCs arising within scars/chronic ulcers, perineural invasion or poor differentiation on histology, immunosuppression
- Organ transplant patients have 65-fold increased risk for developing cutaneous SCC
- Histology: irregular sheets or islands of atypical, brightly eosinophilic squamous cells with nuclear pleomorphism originating from the overlying epidermis and invading the dermis, keratin pearls,  $\pm$  vascular or perineural invasion, necrotic keratinocytes, mitoses
- Variants: acantholytic, adenoid, bowenoid, mucinous, sclerotic, spindle cell, and verrucous
- Treatment: standard excision with margins, Mohs micrographic surgery, electrodesiccation and curettage, radiotherapy

**Figure 5.7****A: Bowen's disease\*****B: SCC arising within DLE\*****C: SCC, lip**

\* Courtesy of Dr. Paul Getz

**Keratoacanthoma (KA)** (Figure 5.8A–C)

- Typically considered to be variant of SCC; may spontaneously regress or occur as multiple lesions
- Presents as rapidly enlarging papule or nodule often appearing crateriform with keratotic center, typically in sun-exposed areas
- Different presentations: solitary, multiple, giant, keratoacanthoma centrifugum marginatum, KA associated with Muir–Torre syndrome (GI cancer and sebaceous neoplasms), generalized eruptive KAs (Grzybowski or Ferguson-Smith type)
  - **KA centrifugum marginatum:** may reach several centimeters in diameter, concomitant expansion of border and central healing
  - **Giant KA:** rapid enlargement of nodule to several centimeters
  - **Ferguson-Smith type:** sudden-onset of multiple KAs in childhood, which will slowly resolve on their own
  - **Grzybowski type:** sudden-onset of multiple KAs in adulthood (eruptive pattern)
- Histology: symmetric tumor with acanthotic epidermis consisting of well-differentiated squamous cells with glassy cytoplasm, central invagination of neoplasm filled with keratin and epithelial lips extending around both sides of crater, prominent inflammatory infiltrate around lesion
- Treatment: complete excision typically performed, observation alone (if lesion following an involutational pattern)

**Basal Cell Carcinoma (BCC)** (Figure 5.9A–C)

- Most common cutaneous cancer
- Transplant patients with 10-fold higher risk
- Multiple variants with specific features
  - **Superficial BCC:** may present as a pink thin plaque with pearly border,  $\pm$  scale,  $\pm$  pigment, commonly seen on trunk or limb; histology shows many superficial buds of basaloid cells limited to superficial dermis, peripheral palisading of nuclei
  - **Nodular BCC:** most common; translucent papule or nodule with overlying telangiectasias,  $\pm$  ulceration,  $\pm$  pigment (small areas of brown pigment), over time borders often become rolled and pearly with central ulceration ('rodent ulcer'); histology shows large islands of basaloid keratinocytes with peripheral palisading within dermis, fibromyxoid stroma, stromal retraction around tumor islands,  $\pm$  necrosis within large tumor islands forming cystic areas
  - **Morpheaform BCC:** indurated firm plaque with ill-defined borders resembling a scar, aggressive growth pattern; histology with strands of basaloid keratinocytes within fibrotic stroma
  - **Metatypical (basosquamous) BCC:** features of both BCC and SCC

Multiple BCCs seen in Gorlin's syndrome



**Figure 5.8**  
**A: Keratoacanthoma**  
 (Courtesy of Dr. Paul Getz)  
**B: Keratoacanthoma**  
**C: Keratoacanthoma**



- **Micronodular:** histology with small tumor islands (smaller than nodular BCC) within fibrous stroma
- **Adenoid BCC:** histology shows pseudoglandular pattern with mucin within basaloid aggregates
- **Cystic BCC:** gray-blue cystic papule or nodule with clear fluid in center; histology shows pools of mucin seen histologically within center of tumor
- **Fibroepithelioma of Pinkus:** rare variant appearing as pink plaque or smooth nodule on lower back; histology with thin anastomosing cords of basaloid cells in fibrous stroma arising from epidermis
- Rarely metastasizes (lymph nodes and lung)
- Treatment: topical imiquimod (for superficial BCCs), surgical excision with margins, Mohs micrographic surgery, curettage and electrodesiccation, radiotherapy

### **Merkel Cell Carcinoma**

- Rare, highly aggressive malignant neuroendocrine carcinoma; 5-year mortality approximately 30%
- Presents as red to pink dome-shaped rapidly growing nodule typically involving head, neck, leg, or buttock; 40% metastasis rate at time of diagnosis
- Histology: poorly defined dermal mass of small blue monomorphic round cells with scanty cytoplasm and nuclear molding, abundant mitotic figures, often see necrosis and crush artifact; “ball in mitt” cellular pattern with crescentic neoplastic cells wrapping around round neoplastic cell; three growth patterns:
  - **Trabecular:** islands of neoplastic cells connecting to one another via anastomosing cords
  - **Intermediate-cell type:** large solid collection of cells with peripheral trabecular pattern
  - **Small-cell type:** diffuse sheet-like infiltration mixed with intermediate cells
- Immunohistochemically: CK20, CK8/18/19 (CAM 5.2), chromogranin, somatostatin, calcitonin, synaptophysin, vasoactive intestinal peptide, neuron-specific enolase
- Treatment: wide local excision (3cm margins) often with adjuvant chemotherapy and/or radiation, sentinel lymph node biopsy



**Figure 5.9**  
**A: Morpheaform BCC**  
**B: Nodular BCC**  
**C: Ulcerated BCC**

**Melanoma** (Figures 5.10A–C and 5.11, Table 5-1)

- Aggressive tumor resulting from melanocytes and affecting younger population (peak age 20–45 years old)
- Risk factors: tendency to sunburn/freckle, light-colored skin/hair/eyes, several nevi, CDKN2A mutation, prior history of melanoma, intermittent high UVR with sunburns in childhood/adolescence, immunosuppression (transplant patients with threefold to fourfold higher risk)
- Four clinical types:
  - **Superficial spreading melanoma (SSM)**: most common (70% in white population); presents as darkly pigmented macule or thin plaque,  $\pm$  notched border, varying shades of brown, possible areas of regression; most common site is back (men) and lower legs (women); horizontal growth
  - **Nodular melanoma (NM)**: second most common type in light-skinned patients, darkly pigmented papule or nodule with rapid onset; vertical growth
  - **Lentigo maligna melanoma (LMM)**: least common; evolves from lentigo maligna, often in sun-exposed sites in older age group; presents as hyperpigmented patch with varying shades of brown, irregular border
  - **Acral lentiginous melanoma (ALM)**: most common type seen in darker-skinned patients; often presents as hyperpigmented patch with varying shades of brown or black and irregular borders
- Histology: asymmetric, poorly circumscribed collection of atypical melanocytes; single melanocytes characteristic and often with pagetoid spread, irregular nests in basal layer and invasion into the dermis, poor maturation of melanocytes,  $\pm$  regression
- Recent guidelines emphasize tumor mitotic rate (TMR) and have incorporated this into existing staging system
- Poor prognostic factors: male gender, increasing age, increased tumor thickness, ulceration, increased TMR, and head/neck/trunk location (vs. extremities)
- Treatment: conventional excision with margins, Mohs micrographic surgery,  $\pm$  sentinel lymph node biopsy (usually for intermediate thickness melanoma of 1–4 mm); advanced cases: interferon- $\alpha$ , interleukin-2, chemotherapy/radiation therapy, vaccine therapy
  - Excision margins for melanoma:
  - Melanoma in situ: 0.5 cm margins
  - Melanoma <2 mm: 1 cm margins
  - Melanoma  $\geq$ 2 mm: 2 cm margins

**Figure 5.10****A: Lentigo maligna\*****B: Melanoma****C: Hutchinson's sign\****\*Courtesy of Dr. Paul Getz*



**Table 5-1 Melanoma Staging**

Stage	TNM	Criteria
0	Tis N0M0	Melanoma in situ
IA	T1a N0M0	≤1.0 mm without ulceration and mitotic rate <1/mm <sup>2</sup>
IB	T1b N0M0 T2a N0M0	≤1.0 mm with ulceration or mitotic rate >1/mm <sup>2</sup> 1.01–2.0 mm without ulceration
IIA	T2b N0M0 T3a N0M0	1.01–2.0 mm with ulceration 2.01–4.0 mm without ulceration
IIB	T3b N0M0 T4a N0M0	2.01–4.0 mm with ulceration >4 mm without ulceration
IIC	T4b N0M0	>4 mm with ulceration
IIIA	T1-4a N1a M0 T1-4a N2a M0	Nonulcerated tumor with single regional nodal micrometastasis Nonulcerated tumor with 2–3 nodal micrometastasis
IIIB	T1-4b N1a M0 T1-4b N2a M0 T1-4a N1b M0 T1-4a N2b M0 T1-4a/b N2c M0	Ulcerated tumor with single regional nodal micrometastasis Ulcerated tumor with 2–3 nodal micrometastasis Nonulcerated tumor with single regional nodal macrometastasis Nonulcerated tumor with 2–3 nodal macrometastasis In-transit met(s) and/or satellite lesion(s) without metastatic LNs
IIIC	T1-4b N2a M0 T1-4b N2b M0 T1-4a/b N3M0	Ulcerated tumor with macrometastasis of one lymph node Ulcerated tumor with macrometastasis in 2–3 lymph nodes Tumor with four or more metastatic nodes, matted nodes or in transit mets/satellite lesion(s) with metastatic nodes
IV	Any T, any N, M1a Any T, any N, M1b Any T, any N, M1c	Distant skin, subcutaneous, or lymph node metastasis Lung metastasis Visceral or any distant metastasis + elevated LDH

**Extramammary Paget's Disease (EMPD)**

- Intraepithelial adenocarcinoma of apocrine gland, histologically and morphologically similar to Paget's disease of the nipple; however, EMPD typically targets genital and perianal skin; can be primary cutaneous adenocarcinoma or can result from spread of in situ or invasive malignancy (secondary EMPD), latter in up to 25% of cases
- Often presents as unilateral, well-demarcated erythematous plaque resembling chronic eczematous dermatitis in perianal or genital area; ensuing pruritus often results in excoriations and lichenification
- Histology: diffuse infiltration of large vacuolated cells with bluish cytoplasm in epidermis (Paget cells) often in lower epidermis, CK20 + (immunohistochemical stains needed to differentiation between pagetoid melanoma)
- Treatment: thorough search for possible concurrent underlying malignancy, surgical excision



**Figure 5.11**  
Melanoma (Courtesy of Dr. Paul Getz)

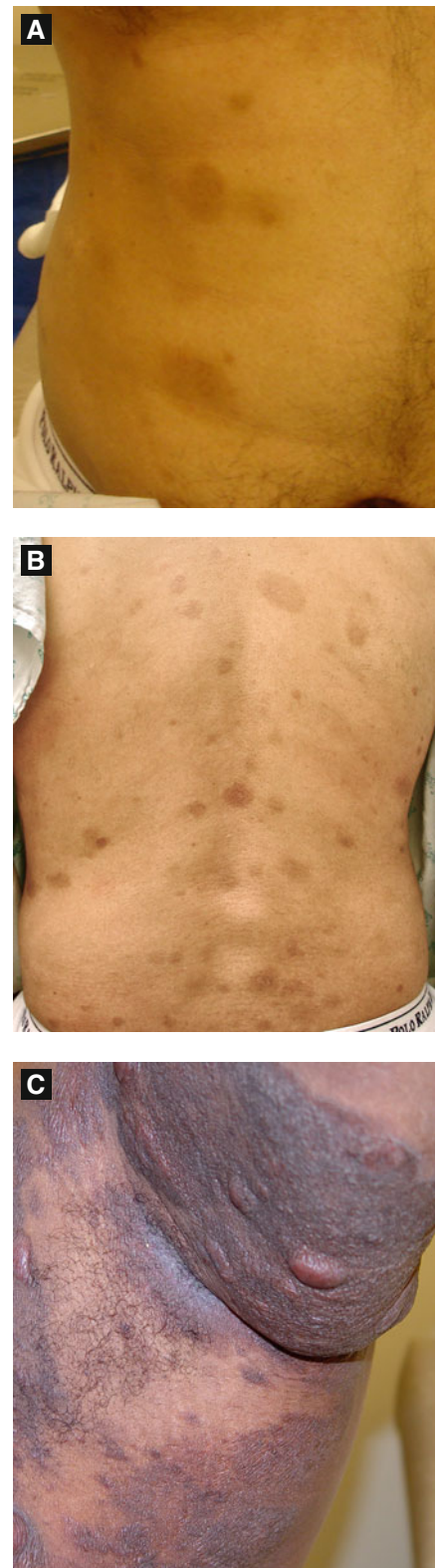
**Cutaneous T-Cell Lymphoma (CTCL, Mycosis Fungoides)**

(Figures 5.12A–C and 5.13A)

- T-cell neoplasm originating in skin; presentation varies based on stage of disease:
  - **Patch stage:** erythematous, violet or hyperpigmented patches (single or multiple) in sun-protected areas such as buttocks, thighs, abdomen
  - **Plaque stage:** well-demarcated irregularly shaped erythematous to violaceous to red-brown plaques in sun-protected areas; often pruritic and asymmetric; may arise de novo or from existing patches
  - **Tumor stage:** enlarging dome-shaped smooth nodules arising either de novo or from existing patches/plaques; aggressive with vertical growth
  - **Sezary syndrome:** triad of generalized lymphadenopathy, pruritic erythroderma, and Sezary cells (large hyperconvoluted lymphocytes); other symptoms often seen include alopecia, nail dystrophy, pruritus, and scaling of palms/soles
- Histology: epidermis may be acanthotic, atrophic or ulcerated, single cell exocytosis or epidermotropism of atypical lymphocytes into epidermis with Pautrier microabscesses (collection of atypical lymphocytes with cerebriform nuclei), diffuse or band-like mononuclear cell infiltrate with hyperchromatic cerebriform nuclei
- May need multiple biopsies before characteristic changes seen; atypical T cells typically negative for CD7 T-cell marker
- Treatment may be skin directed or systemic depending on stage of disease
  - Topical: corticosteroids or mechlorethamine (nitrogen mustard)
  - Phototherapy (PUVA, NBUVB)
  - Localized radiotherapy
  - Electron beam therapy
  - Photophoresis: typically for erythrodermic MF
  - Immunosuppressants: methotrexate, interferon- $\alpha$
  - Bexarotene
  - Denileukin diftitox
  - Chemotherapy

**Lymphomatoid Papulosis (LyP) (Figure 5.13B, C)**

- Chronic papulonecrotic condition with self-healing nature; recurrent crops of lesions at different stages of development that spontaneously heal over 1–2 months on trunk and limbs, leaving oval slightly depressed scars
- Controversy over whether LyP is a benign disorder of activated T cells responding to internal/external stimuli or if indolent T-cell malignancy of skin; most likely low-grade malignant CTCL; chronic, indolent course in most patients and prognosis is usually excellent
- Presents as erythematous necrotic papules, papulopustules, necrotic eschars or papulovesicles
- Histology: wedge-shaped dense dermal infiltrate consisting of lymphoid cells with numerous neutrophils, eosinophils, and atypical lymphocytes (latter may be 50% of cells),  $\pm$  epidermotropism, atypical T cells characteristically stain positive with CD30-positive (Ki-1)
- Treatment: no curative benefits; low dose weekly methotrexate, PUVA, high potency topical steroid (to hasten resolution of lesions), topical nitrogen mustard

**Figure 5.12****A: CTCL, patch stage\*****B: CTCL, patch stage\*****C: CTCL, plaque stage\***

\*Courtesy of Dr. Sophie M. Worobec

### **Microcystic Adnexal Carcinoma**

- Locally aggressive sweat duct carcinoma uncommonly seen in young or middle-aged adults
- Presents as indurated plaque resembling sclerosing BCC often in perioral, perinasal, periorbital, or lip area
- Histology: ill-defined neoplasm in dermis and subcutaneous tissue with islands of basaloid cells with small lumina and horn cysts in background of hyalinized fibrotic stroma,  $\pm$  perineural invasion; of note, only rarely see cytologic atypia; appears more like syringoma in upper half and cord-like in lower half of tissue specimen
- Treatment: conventional excision or Mohs surgery; high recurrence rate

### **Mucinous Carcinoma**

- Rare adnexal tumor likely from eccrine gland
- Often presents as slow-growing nodule, ulcer, or cyst with low metastatic potential, often seen on head or neck
- Histology: islands of floating ductal structures in a lake of mucin, cells with eosinophilic cytoplasm and hyperchromatic nuclei, mucin separated by thin fibrocollagenous septae
- Must differentiate primary mucinous carcinoma from metastatic tumors (especially breast or GI origin)
- Treatment: local excision; high rate of recurrence



**Figure 5.13**

**A: CTCL, tumor stage\***

**B: Lymphomatoid papulosis\***

**C: Lymphomatoid papulosis\***

*\*Courtesy of Dr. Sophie M. Worobec*



**Angiosarcoma** (Figure 5.14A)

- Very aggressive but rare tumor presenting as violaceous plaque on face or scalp; may be solitary or multiple and most often seen in elderly men; metastasis seen in lymph nodes, lungs, spleen, and liver
- Angiosarcoma may occur in presence of chronic lymphedema; Stewart-Treves syndrome: angiosarcoma occurring in area of long-standing chronic lymphedema (lymphedema often resulting from radical mastectomy to treat breast cancer)
- Histology: poorly demarcated tumor consisting of dissecting vascular spaces with large pleomorphic, hyperchromatic endothelial cells, extravasated red blood cells, + CD31, + CD34, + factor VIII-related antigen
- Poor prognosis; treat with wide surgical excision but high rate of recurrence, ± adjunctive radiation therapy

**Sebaceous Carcinoma** (Figure 5.14B)

- Erythematous pearly nodule or plaque often seen in the periorbital area (eyelid)
- Histology: asymmetric, poorly circumscribed lobules of basaloid or squamoid cells and poorly developed atypical sebaceous cells (moderate to severe atypia)
- Significant metastatic potential
- May be seen in Muir-Torre syndrome

**Figure 5.14****A: Angiosarcoma**

(Reprint from Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases*. New York, NY: Springer; 2007)

**B: Sebaceous carcinoma**

(Reprint from Markman M, ed. *Atlas of Cancer*. Philadelphia: Current Medicine Inc; 2002)



**Dermatofibrosarcoma Protuberans (DFSP)** (Figure 5.15A, B)

- Uncommon neoplasm often due to chromosomal abnormality: characteristic reciprocal translocation t(17;22)(q22;q13) resulting in fusion of collagen 1 $\alpha$ 1 and platelet-derived growth factor B (COL1A1-PDGFB), a fusion oncogene; this is the basis for treating such tumors with PDGF inhibitor like imatinib (Gleevec®)
- Presents as slow-growing large nodule or plaque with multiple protuberances, commonly on trunk (followed by extremities) in middle-aged adults
- Histology: ill-defined dense cellular proliferation of monomorphic spindle-shaped fibroblasts in storiform or cartwheel pattern, cells often with mild-to-moderate atypia;  $\pm$  may infiltrate subcutaneous fat in fascicular pattern (honeycomb appearance); + CD34 but negative factor XIIIa (allowing differentiation from DF)
- Treatment: Mohs surgery or wide local excision (frequently recurs with latter)  $\pm$  adjuvant radiotherapy

**Malignant Fibrous Histiocytoma (MFH)**

- Presents as deep mass in subcutaneous tissue
- Histology: subcutaneous cellular proliferation with histiocytes, several bizarre giant cells and fibroblasts, highly atypical mitoses present
- High risk of metastasis

**Atypical Fibroxanthoma (AFX)** (Figure 5.15C)

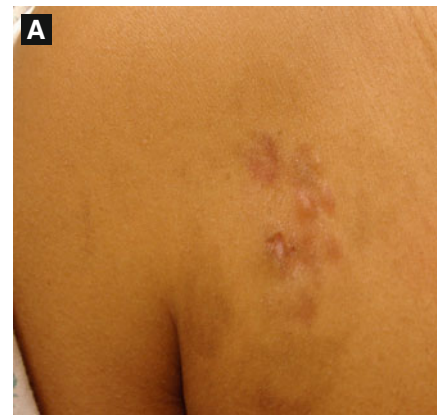
- Superficial variant of MFH; low-grade sarcoma typically in elderly patients with small risk of metastasis
- Presents with red nodule or plaque on sun-damaged skin with frequent ulceration
- Histology: cellular proliferation in dermis consisting of bizarre spindle cells, epithelioid cells, and multinucleated giant cells,  $\pm$  foamy cells, many atypical mitoses and severe pleomorphism seen, prominent solar elastosis

**Epithelioid Sarcoma**

- Presents as slow-growing firm subcutaneous nodule often involving distal extremities (hands) in young adults
- Histology: poorly circumscribed nodular proliferation of spindle-shaped, round, or polygonal pleomorphic cells with eosinophilic cytoplasm frequently seen palisading around central necrotic zone, many atypical mitoses, neoplasm typically associated with fascia
- Often recurs (50% risk of metastasis)

**Leiomyosarcoma**

- Superficial malignant smooth muscle tumor
- Presents as solitary or multiple deep nodules with rapid enlargement or ulceration; predilection for head, neck, or extremities
- Histology: ranges from well-differentiated neoplasm with resemblance to leiomyoma to poorly differentiated neoplasm with liking to atypical fibroxanthoma; more cellular with atypia and mitoses than in leiomyoma
- Prognosis excellent; dermal lesions rarely metastasize but subcutaneous lesions may (up to 30–40% of cases)
- Treatment: complete excision

**Figure 5.15****A: DFSP, chest**

(Courtesy of Dr. Sophie M. Worobec)

**B: DFSP**(Reprint from Markman M, ed. *Atlas of Cancer*. Philadelphia: Current Medicine Inc; 2002)**C: Atypical fibroxanthoma**(Reprint from Bologna JL, Rapini R, Jorrizo JL. *Dermatology*. 2nd ed. St. Louis, MO: Mosby; 2008)

### Liposarcoma

- Exceedingly rare; presents as deep-seated often asymptomatic nodule
- Histology: neoplasm in subcutaneous fat and consists of lipid-containing cells with variable differentiation toward adipose cells

## 5.3 CYSTS

Entity	Clinical Findings	Histologic Findings
<b>Epidermal Inclusion Cyst</b> (Epidermoid cyst)	Well-demarcated skin-colored nodule, ± visible central punctum	Cyst lined by stratified squamous epithelium with <u>granular layer</u> and contains lamellated keratin; multiple cysts in Gardner syndrome
<b>Pilar Cyst</b> (Trichilemmal cyst)	Clinically indistinguishable from EIC but located on scalp, frequently multiple	Lined by stratified squamous epithelium, <u>no granular layer</u> , cyst contains homogenized keratin, ± foci of calcification
<b>Proliferating Trichilemmal Cyst</b>  Neoplastic cells undergoing trichilemmal keratinization	Slow-growing nodule on scalp	Well-circumscribed nodule in deep dermis with solid and cystic patterns, neoplastic cells with some degree of hyperchromasia and mitotic figures, “horn pearls,” foreign body giant cell reaction, tumor with <u>pushing margins</u> , ± foci of calcification
<b>Dermoid Cyst</b>	Congenital cyst often on face (often <b>lateral eyebrow</b> )	Lined by squamous epithelium with granular layer and cyst contains lamellated keratin and ± hair shafts, multiple <u>pilosebaceous units</u> appear near cyst lining
<b>Vellus Hair Cyst</b>	Tiny dome-shaped skin-colored to pigmented papules on trunk in children	Lined by squamous epithelium with granular layer and cyst contains lamellated keratin and ± <u>vellus hairs</u>
<b>Steatocystoma</b>	Dermal skin-colored to yellow nodule in dermis that drains oily fluid if punctured, common in chest, axilla, and groin	Cyst lined by stratified squamous epithelium with granular layer with thin, <u>corrugated eosinophilic cuticle</u> , adjacent <u>sebaceous lobules</u> next to cyst wall  Multiple seen in steatocystoma multiplex
<b>Hidrocystoma</b>	Translucent, skin-colored to bluish cyst commonly on face	Unilocular or multilocular cyst lined by layers of epithelial cells and luminal decapitation secretion, cyst appears empty
<b>Bronchogenic Cyst</b>	Solitary cyst mainly in suprasternal notch or anterior neck at birth	Lined by pseudostratified ciliated columnar epithelium with interspersed goblet cells, cyst lining often surrounded by <u>smooth muscle</u> , mucous glands, cartilage, or <u>lymphoid follicles</u>
<b>Thyroglossal Duct Cyst</b>	Cystic nodule commonly over <b>midline anterior neck</b> in children or young adults	Lined with cuboidal, columnar, or stratified squamous epithelium, may contain some ciliated columnar cells, characteristic <u>thyroid follicles in cyst wall</u> (low cuboidal cells surrounding pink homogenous material)
<b>Branchial Cleft Cyst</b>	Congenital cyst often arising on <b>lateral neck</b> ; due to incomplete involution of branchial cleft structures	Lined by stratified squamous epithelium or pseudostratified ciliated columnar epithelium, surrounded by <u>lymphoid tissue</u> ; prudent to delineate extent of lesion by <u>CT</u> or <u>MRI</u> before cyst removal
<b>Auricular Pseudocyst</b>	Fluid-filled cavity in the cartilaginous portion of ear	Intracartilaginous cavity without epithelial lining, surrounding <u>degenerated cartilage</u> and hyalinized material

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# 6

## Dermatologic Surgery

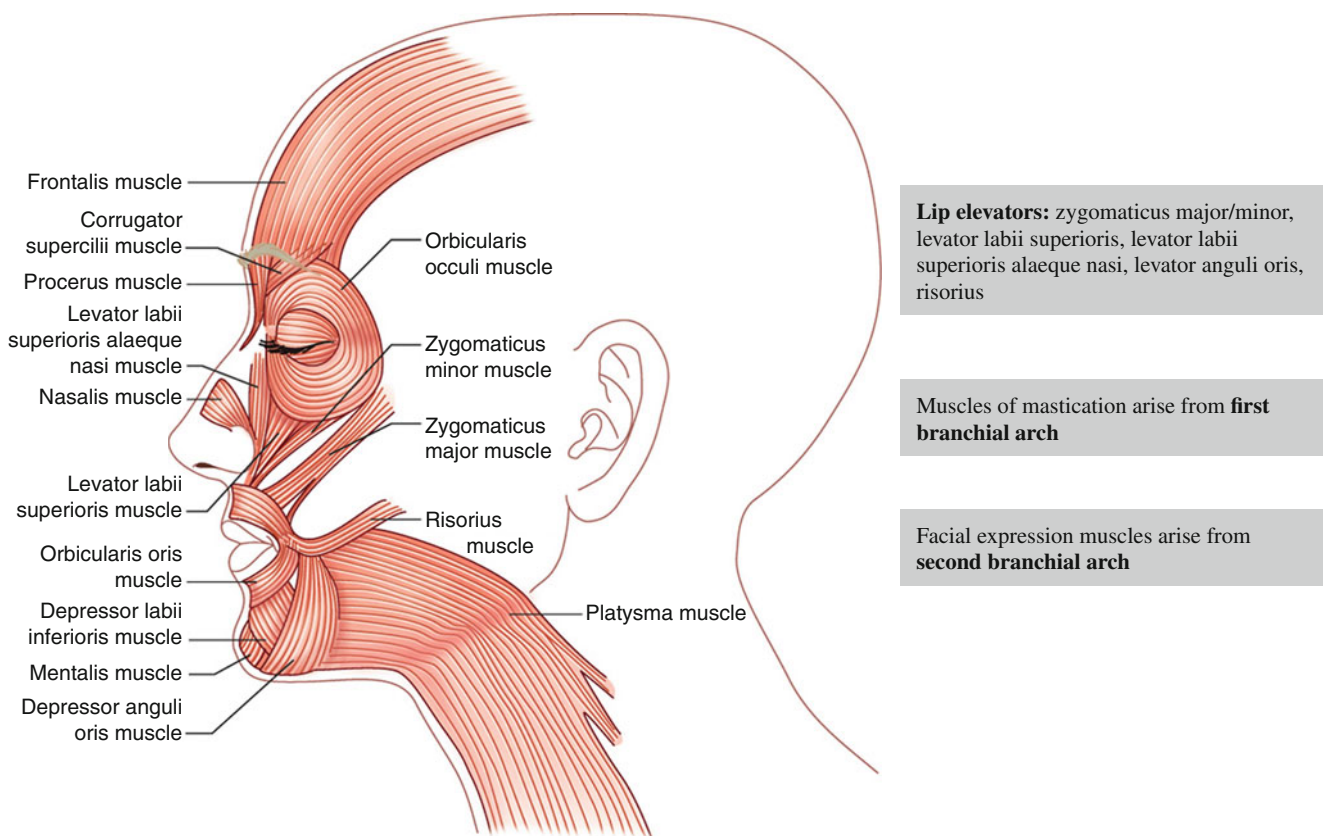
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## 6.1 SURGICAL ANATOMY

### A. Anatomy of Head and Neck Muscles (Figure 6.1)

- Know function of specific function and innervation of head/neck muscles (Table 6-1)
- Location-specific layers:
  - Scalp has five layers: epidermis/dermis, subcutaneous tissue, musculoaponeurotic layer, loose subaponeurotic tissue and periosteum
  - Facial layers: epidermis, dermis, subcutaneous fat, SMAS and periosteum
- Superficial musculoaponeurotic system (SMAS)
  - Superficial fibromuscular layer enclosing facial muscles of face/neck; extends from frontalis muscle superiorly to platysma muscle inferiorly, temporalis muscle laterally
  - Allows organized movement of regional muscles during contraction and contributes to appearance of skin tension lines
  - Protective anatomic plane as sensory nerves and axial blood vessels typically located within or between SMAS and subcutaneous fat; motor nerves usually deep to SMAS
  - During facelift, SMAS plicated or pulled to draw skin tight
  - Equivalent of SMAS on scalp is galea aponeurotica, which is a thick inelastic membrane and ideal plane to undermine as it is relatively avascular, separates easily, and results in decreased trauma to neurovascular structures
- Dissection planes (Table 6-2)
  - Undermining should always take place above SMAS with few exceptions



**Figure 6.1**

**Muscles of the head and neck** (Reprint from Nouri, K. *Complications in Dermatologic Surgery*. Philadelphia, PA: Mosby Elsevier; 2008)

**Table 6-1 Muscles of Head and Neck**

Muscle	Function	Innervation
<b>Occipitalis</b>	Pulls scalp posteriorly	Posterior auricular br. of facial nerve (CN VII)
Do not confuse with postauricular branch of trigeminal nerve (CNV)		
<b>Frontalis muscle</b>	Elevates eyebrows and wrinkles forehead (horizontal forehead lines)	Temporal br. of CN VII
<b>Orbicularis oculi</b>	Blinking and tight closure of eyelids ("crow's feet"), lesser role as brow depressor (depressor supercilii)	Temporal br. of CN VII (upper portion), zygomatic branch of CN VII (lower portion)
<b>Corrugator supercilii</b>	Pulls eyebrows medially and downward (vertical glabellar lines)	Temporal br. of CN VII
<b>Procerus</b>	Pulls medial portion of eyebrows and glabellar skin downward (horizontal glabellar lines over root of nose)	Zygomatic and buccal br. of CN VII per Bologna (rare sources say temporal br.)
<b>Nasalis</b>	Alar flaring and compression ("bunny lines" over upper bridge of nose)	Zygomatic and buccal br. of CN VII
<b>Levator labii superioris</b>	Elevates upper lip	Buccal br. of CN VII
<b>Levator labii superioris alaeque nasi</b>	Lifts upper lip, <b>dilates nostrils</b>	Buccal br. of CN VII
<b>Levator anguli oris</b>	Lifts <b>corners of the mouth</b>	Buccal br. of CN VII
<b>Risorius</b>	Produces smile by drawing back corners of mouth	Marginal mandibular br. of CN VII per Bologna (other sources say buccal br.)
<b>Zygomaticus major</b>	Main contributor to smile: elevates and draws corner of mouth laterally	Buccal br. of CN VII
<b>Zygomaticus minor</b>	Elevates upper lip	Buccal br. of CN VII
<b>Modiolus</b>	Accounts for cheek <b>dimples</b> in some patients	
<b>Orbicularis oris</b>	Closes and purses lips (vertical perioral lip lines)	Buccal or marginal mandibular br. of CN VII
<b>Buccinator</b>	Presses cheek against teeth, allows <b>blowing of cheeks</b>	Buccal br. of CN VII
<b>Depressor anguli oris</b>	Pulls <b>corner of mouth downward</b> (marionette lines → vertical lines at oral commissure)	Marginal mandibular (MM) br. per Bologna (most other sources say both MM and buccal br.)
<b>Depressor labii inferioris</b>	Depresses lower lip	Marginal mandibular br. CN VII
<b>Mentalis</b>	<b>Protrudes lower lip</b>	Marginal mandibular br. CN VII
<b>Platysma</b>	Pulls corner of mouth inferiorly, tenses neck (horizontal neck lines)	Marginal mandibular br (upper portion) and cervical br. CN VII

**Table 6-2 Dissection Planes in Head and Neck**

Location	Plane of Dissection
Face	<b>Superficial to SMAS:</b> superficial to mid fat (more superficial in high-risk areas like zygomatic arch, temporal fossa, etc.)
Nose	<b>Deep to SMAS:</b> superficial to periosteum or perichondrium (below nasalis muscle)
Scalp	Subgaleal plane: superficial to periosteum (below galea aponeurotica), relatively avascular space
Trunk/limbs	Deep fat if small excision; just above deep fascia if larger excision

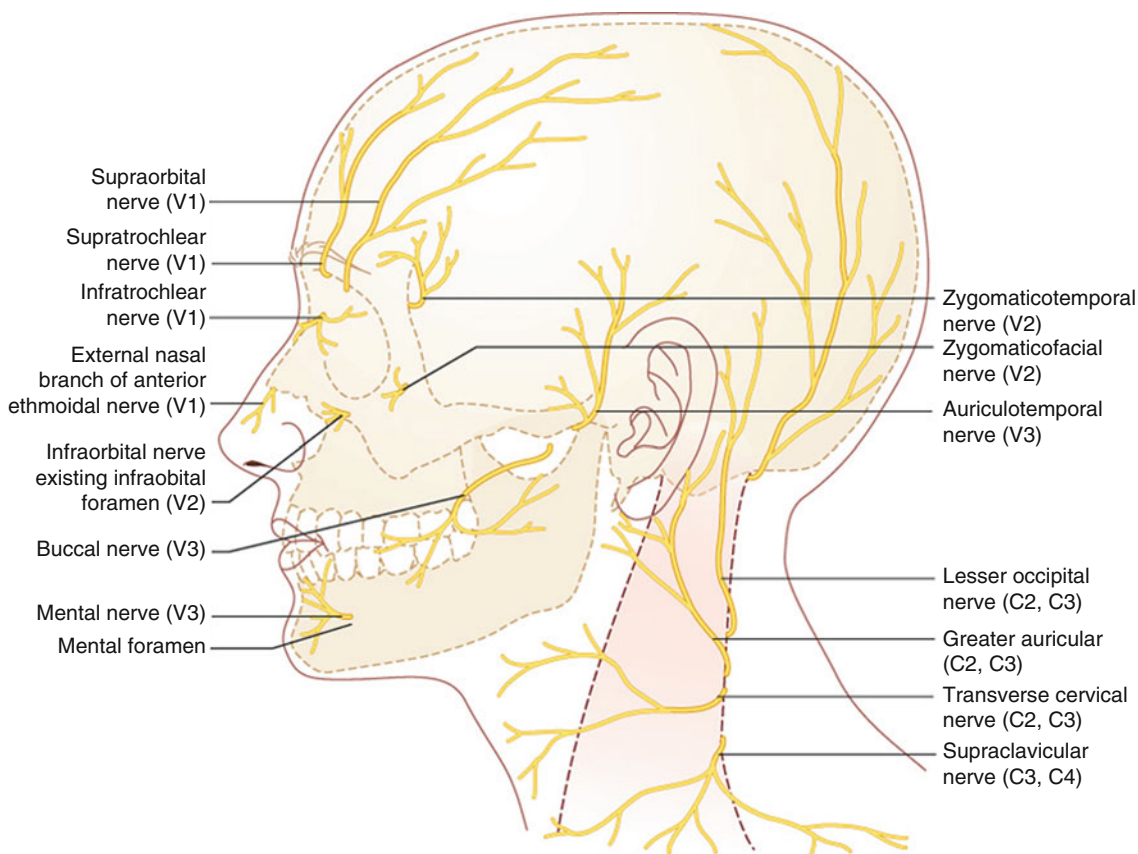
**B. Sensory Innervation of Head and Neck** (Figures 6.2 and 6.3B, Table 6-3)

- Trigeminal nerve provides sensory innervation to facial skin along with motor function to muscles of mastication (masseter, medial/lateral pterygoid, temporalis)
  - Three main trigeminal divisions: V1 (ophthalmic), V2 (maxillary), and V3 (mandibular)
  - V1 with five subdivisions: supraorbital (frontal branch), supratrochlear (frontal branch), infratrochlear (nasociliary branch), external nasal (nasociliary branch), and lacrimal nerve

**Trigeminal trophic syndrome:**

injury of CN V (gasserian ganglion), results in dysesthesia often involving nasal ala resulting in sickle-shaped ulceration, treat w/ amitriptyline or carbamazepine

**Frey's syndrome:** injury to auriculotemporal branch of CN V in parotid region (carries sympathetic fibers to sweat glands in scalp and parasympathetic fibers to parotid gland), haphazard regeneration leads to redness (vasodilation) and hyperhidrosis of ipsilateral cheek when eating

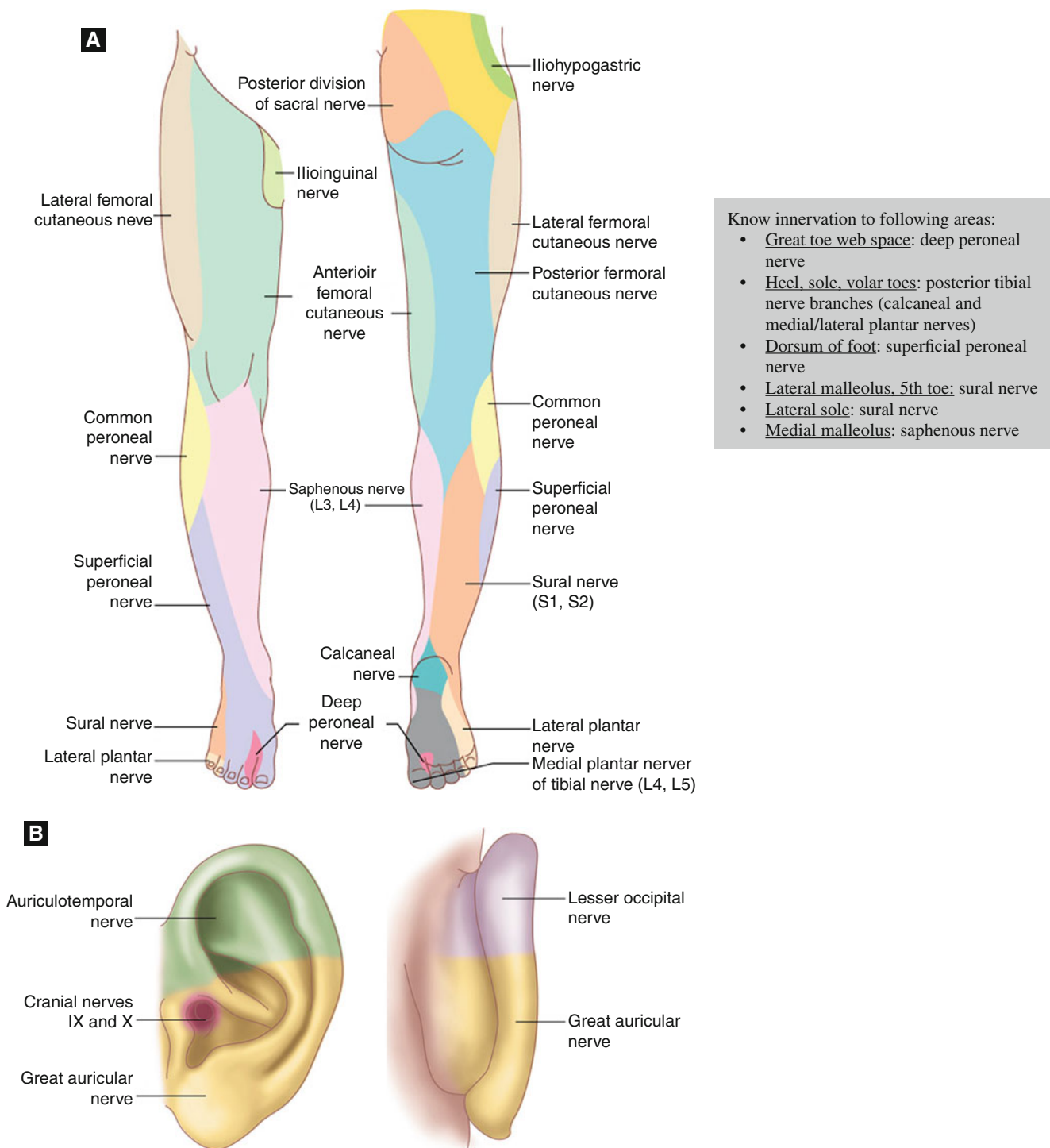
**Figure 6.2****Sensory innervation of head and neck**

(Reprint from Nouri, K. *Complications in Dermatologic Surgery*. Philadelphia, PA: Mosby Elsevier; 2008)



**Table 6-3 Sensory Innervation of Head and Neck**

Nerve Branch	Sensory Innervation to:	
V1: Ophthalmic branch		
Supratrochlear nerve	Medial forehead, medial upper eyelid, frontal scalp	
Supraorbital nerve	Most of forehead, portion of frontoparietal scalp, frontal sinus, upper eyelid	
Lacrimal nerve	Lacrimal gland, conjunctivae, lateral eyelids	Reason why zoster lesions on tip of nose can be sign of ocular involvement (since both ciliary branch and external nasal branch come from nasociliary nerve)
External nasal branch of anterior ethmoidal (AE) nerve	<b>Nasal dorsum, tip, supratip, and columella</b> CN V → ophthalmic → nasociliary → AE nerve → external nasal branch	
Ciliary nerve	Corneal surface CN V → ophthalmic → nasociliary → ciliary nerve	
Infratrochlear nerve	<b>Root of nose, upper lateral sidewalls</b> , part of medial canthus, lacrimal sac	
V2: Maxillary branch		
Infraorbital nerve	Medial cheek, upper lip, <b>lower nasal sidewall, nasal ala</b> , lower eyelid	
Zygomaticofacial (ZMF) nerve	Malar eminence of cheek	
Zygomaticotemporal (ZMT) nerve	Temple and supratemporal scalp	
Superior alveolar and palatine nerve	Upper teeth, palate, nasal mucosa, and gingiva	
V3: Mandibular branch (both sensory and motor branches)		
Auriculotemporal nerve	Anterior upper half of ear, <b>tragus, preauricular cheek</b> , anterior ½ of meatus, TMJ, external <b>tympanic membrane</b> , temple, temporoparietal scalp	
Buccal nerve	Cheek, buccal mucosa, and gingiva	
Inferior alveolar	Mandibular teeth	
Mental nerve	Chin, lower lip	
Lingual nerve	Anterior 2/3 of tongue (somatic sensation), floor of mouth, lower gingiva	
Cervical plexus (C2–C4)		
Lesser occipital nerve C2	Neck and postauricular scalp, posterior upper half of ear	
Greater occipital nerve C2	Occipital scalp	
Transverse cervical nerve C2 and C3	Anterior neck	
Supraclavicular nerve C3 and C4	Anterior chest, clavicle, and shoulder	
Greater auricular nerve C2 and C3	Lateral neck, <b>angle of jaw</b> , inferior lateral cheek, anterior/posterior lower half of ear (include ear lobule), mastoid process, and postauricular skin	
Other sensory nerves		
Facial nerve	CN VII → chorda tympani  CN VII → small branches (minor role in sensory)	Taste sensation (anterior 2/3 tongue via chorda tympani), small portion of auditory meatus, concha bowl (variably innervated by branches of vagus and facial nerves), soft palate, pharynx
Auricular branch of vagus nerve (CN X)	CN X → auricular branch	Posterior ½ of tympanic membrane and posterior wall of external auditory meatus
Glossopharyngeal (CN IX)		Taste and somatic sensation to posterior 1/3 of tongue



**Figure 6.3**

**A: Sensory innervation of the lower extremity**

**B: Sensory innervation of the ear**

(Reprint from Nouri, K. *Complications in Dermatologic Surgery*. Philadelphia, PA: Mosby Elsevier; 2008)

### C. Motor Innervation of Head and Neck

Mnemonic for CN VII branches: **To Zanzibar by Motor Car**

- Facial nerve exits skull via stylomastoid foramen, enters parotid gland, and then divides into five branches: temporal, zygomatic, buccal, marginal mandibular, and cervical
- Facial nerve innervates muscles of facial expression (motor) and small component sensory innervation (external auditory meatus, anterior tongue)
- All motor nerves innervate respective muscles on muscle's underside with few exceptions
- Three danger zones areas in head/neck for motor nerve injury (Table 6-4)

**Table 6-4 Danger Zones for Motor Nerve Injury**

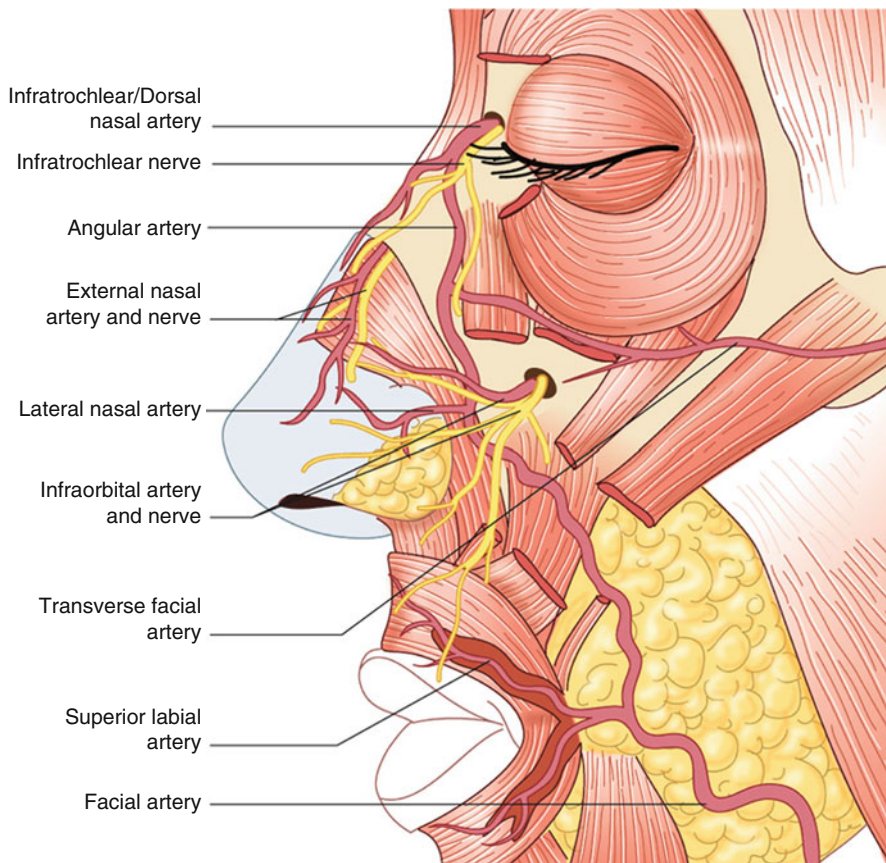
Nerve	Location	Function	Deficiency
Spinal accessory nerve (CN XI)	Nerve courses within posterior triangle of neck in superficial plane, emerges posterior to sterno-cleidomastoid (SCM) within 2 cm of Erb's point  Erb's point: midpoint of posterior border of SCM (point where cervical plexus emerges)	Innervates trapezius muscle	<b>Shoulder drooping, winged scapula</b> , inability to abduct arm
Temporal branch of facial nerve (CN VII)	Nerve courses from a point located 0.5 cm inferior to the tragus to a point 2 cm superior and lateral to tail of eyebrow before diving beneath frontalis muscle  Danger zone between following two lines: ear lobe to lateral edge of eyebrow and tragus to lateral highest forehead crease – nerve most superficial over bony prominence	Innervates frontalis muscle	Inability to raise eyebrow, drooping of ipsilateral eyebrow, inability to close eye completely
Marginal mandibular branch of facial nerve (CN VII)	Most susceptible to injury anterior to angle of mandible during undermining due to superficial location over bony prominence	Innervates lip depressors	Asymmetry with resultant crooked smile and drooling on affected side

### D. Arterial Supply of Head and Neck (Figure 6.4, Table 6-5)

- Vascular supply from external and internal carotid artery

**Table 6-5 Arterial Supply to Head/Neck**

External Carotid Artery (ECA) Branches	Internal Carotid Artery (ICA) Branches
1. <u>Facial artery</u> (terminates by medial canthus) <ol style="list-style-type: none"> <li>Angular artery</li> <li>Superior labial artery</li> <li>Inferior labial artery</li> <li>Lateral nasal artery</li> </ol> 2. <u>Superficial temporal artery</u> <ol style="list-style-type: none"> <li>Transverse facial artery</li> <li>Middle temporal artery</li> <li>Anterior auricular artery</li> <li>Frontal branch</li> <li>Parietal branch</li> </ol> 3. <u>Maxillary artery</u> <ol style="list-style-type: none"> <li>Infraorbital artery</li> <li>Buccal artery</li> <li>Inferior alveolar artery</li> </ol> 4. <u>Occipital artery</u> 5. <u>Posterior auricular artery</u> 6. <u>Lingual artery</u>	1. <u>Ophthalmic artery</u> <ol style="list-style-type: none"> <li>Lacrimal</li> <li><b>Supratrochlear (frontal) artery</b> → Axial blood supply for midline forehead flap; success of flap depends on preservation of this artery</li> <li>Supraorbital artery</li> <li>Posterior ethmoidal</li> <li>Anterior ethmoidal</li> <li><b>Dorsal nasal artery</b> → Anastomosis with angular artery of ECA</li> <li>Anterior ciliary artery</li> <li>Central retinal artery</li> </ol>



Of note, facial artery runs superficially across lower border of mandible and then travels toward nose as angular artery

**Figure 6.4**

**Vascular supply to face**

(Reprint from Nouri, K. *Complications in Dermatologic Surgery*. Philadelphia, PA: Mosby Elsevier; 2008)

## E. Lymph Nodes of the Head and Neck

Lymph Node Location	Locations Drained by Respective Lymph Nodes
<b>Postauricular nodes</b>	Upper posterior ear, mastoid, posterior parietal, and temporal scalp
<b>Occipital nodes</b>	Posterior aspect of scalp
<b>Parotid nodes</b> (includes preauricular and infra-auricular nodes)	Upper and lateral face: frontolateral scalp, anterior surface of ears, lower cheeks, forehead, lateral canthal area
<b>Submental nodes</b>	Central and lower face: central lower lip, chin, floor of mouth, anterior tongue, and chin
<b>Submandibular nodes</b>	Central and lower face: gingival and mucous membranes, lower eyelids, anterior two-thirds of tongue, lips, nose, medial cheeks

Lymphatic drainage of face in downward diagonal direction

## 6.2 EXCISIONS, FLAPS, AND GRAFTS

### A. Excisions

#### Basic Excision Principles

- Fusiform excision with length typically three times longer than width; sides of wound should be vertical with a flat, even wound base at the level of subcutaneous fat or fascia
- Excision should always be made parallel to skin tension lines for best cosmetic result



- Skin tension lines: fine wrinkles seen in aged face typically perpendicular to underlying long axis of muscle; lines from tension exerted on skin by facial expression muscles, collagen, and elastic fibers
- Variants of elliptical excision can be used in particular locations for a better cosmetic result:
  - **S-plasty or lazy S repair**: performed if excision over convex surfaces (i.e., jaw, shin, forearm) to ↓ contraction and buckling along length of scar for better cosmetic result
  - **M-plasty**: effective for reducing length of scar when it would encroach on important structures (i.e., corner of mouth, eyebrow)
  - **Crescent excision**: results in shorter curvilinear scar and can be oriented along curved skin tension lines or cosmetic subunit junction lines (i.e., cheek, chin)
- Of note, lesions on the lip with a size equal or less to 1/3 the length of lower lip can be repaired with primary closure after wedge excision due to laxity of the lip

## Cosmetic Subunits

- Major structural areas of face separated by contour lines or boundaries
- Units arranged by similarity in topographic anatomy, texture, pigmentation, amount of sun exposure, sebaceous gland, and hair type/density
- Major units: forehead, temples, eyelids, nose, cheeks, upper and lower lips, chin and ears
- Units within nose: dorsum, nasal sidewall, soft triangle, tip, alar lobule, columella
- Contour lines between cosmetic units is an ideal place to hide surgical scars (i.e., hairline, alar or nasolabial crease, eyebrows, philtrum, vermilion cutaneous interface)
- Defects should be repaired with tissue from within the same cosmetic unit to preserve consistency and for best cosmetic outcome

## Wound Healing

Wounds may contract as fast as 0.75 mm/day

- Primary versus secondary intention healing
  - Primary intention: direct closure of wound by approximating wound edges together (side-to-side closure, flaps, grafts)
  - Secondary intention: wound left open and allowed to heal from inner to outer surface
- Wound contraction (maximal at 2 months after reepithelialization)
  - Concave skin wounds (i.e., inner ear, nasal alar crease, temple) heal with best with secondary intention (vs. primary)
  - Convex surfaces (i.e., malar cheek, vermilion border of lip, tip of nose) not optimal for healing by secondary intention and may cause ectropion or eclabion in areas with free margin of skin (nose, eyelids)
- Wound healing: four sequential overlapping stages
  - **Vascular phase**: thrombin/exposed collagen results in stimulation of platelets, which release PDGF and other factors important for angiogenesis and fibroplasia → platelets aggregate forming hemostatic plug and damaged vessels are pressed together causing adherence to one another → overall result is hemostasis
  - **Inflammatory phase**: neutrophils (first cell to arrive, often within first hour after injury) and macrophages (most important cell in healing process) recruited to wound site, phagocytosis of debris/bacteria
  - **Proliferative phase**: reepithelialization within first 24 h of injury, production of collagen (type III); macrophages release fibronectin (which attracts fibroblasts) and other factors which induce angiogenesis and granulation tissue formation
  - **Wound contraction and remodeling**: contraction via myofibroblasts, maximum strength of scar reached is 70–80% of original strength prior to injury

Scar strength: **5% at 2 weeks**   **15% at 3 weeks**   **40% at 6 weeks**   **80% at 1 year**

**Table 6-6 Types of Superficial Repair**

Repair	Pros	Cons	Use for:
Simple interrupted	+ provides wound eversion + allows high-low correction + individual sutures may be removed without disturbing remaining sutures	– ↑ overall closure time – ↑ net suture bulk with more prominent suture marks, skin irritation	
Running	+ ↓ closure time + suture bulk spread over entire wound	– integrity depends solely on knots on either end	Use with minimal tension wounds
Vertical mattress	+ relieves tension + wound eversion	– tendency to leave permanent suture marks	High tension areas
Horizontal mattress	+ ↑ holding tension + wound eversion + hemostasis	– ↑ tissue ischemia – railroad track marks	Tight situation where vertical mattress not possible
Running subcuticular	+ avoids any suture marks along skin surface	– ↑ reactivity – ↑ overall closure time	Minimal tension and mobility
Best with polypropylene glycol due to ↓ tissue reactivity			

**B. Flaps**

- May be classified based on:
  - Blood Supply
    - Axial pattern flap-relies on specific artery for blood supply
    - Random pattern flap
  - Primary Motion
    - Advancement
    - Rotation
    - Transposition
- Flaps can redirect wound tension vector and recruit tissue laxity from adjacent skin
- Be able to identify type of flap based on outline of scar (Table 6-7)



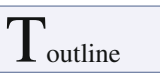








**C. GRAFTS**

- Skin completely detached from donor site; full-thickness, split-thickness, and composite

**Full-Thickness Skin Graft (FTSG)**

- Epidermis + full-thickness dermis
- Advantages: better overall cosmesis (compared to STSG), less wound contracture, retention of appendages
- Disadvantages: increased metabolic demand (due to increased thickness) thus size of FTSG limited, increased rate of graft failure since more vulnerable to necrosis
- Donor sites: preauricular, postauricular, conchal bowl, nasolabial, supraclavicular, inner arm
- Typically FTSGs placed over convex and concave sites (i.e., medial canthus, helix, nasal tip, and nasal ala); must remove fat as this may compromise viability of graft
- Graft should be 10–20% larger than defect size to prevent undersized graft and account for graft contracture (typically up to 15% contraction)
- One week postop: violaceous appearance (resist debridement even if black and potentially necrotic) → monitor site for another week as even if necrotic, can serve as biologic dressing
- Two weeks postop: often changes from a violaceous to pink color

**Table 6-7 Types of Flaps: Advancement, Rotation, and Transpositional**

Type of Flap	Description	Appearance
<b>Advancement flap</b>		
Unidirectional, uncomplicated advancement of leading edge of flap		
Unilateral advancement flap (U-plasty)	Defect excised as square and incision extended in same direction on two but opposite parallel sides of defect; burow's triangle created at end of each extension and flap slides over defect creating U-shaped scar	 outline
Bilateral advancement flap (H-plasty)	Double U-plasty or double advancement flap; two U-plasty flaps created as mirror images of one another; most useful for scalp and eyebrow defects (H-plasty)	 outline
Bilateral T-plasty (A-T, O-T)	Linear repair of wound perpendicular to preexisting cosmetic boundary; useful for above brow, upper cutaneous lateral lip	 outline
Burow's advancement flap	Defect excised in shape of equilateral triangle and one arm of triangle extended; burow's triangle created at contralateral side of extension and tissue slides to cover defect	 outline
Island pedicle flap	Special advancement flap: most of vascular supply from a subcutaneous pedicle (remains attached to central portion of flap) and all dermal margins of flap severed before advanced	 outline
<b>Rotation flap</b>		
Recruits adjacent tissue laxity and directs wound tension vectors away from primary surgical defect; curvilinear incision (arc) adjacent to primary defect and flap rotated to primary defect site; useful for scalp, temple, and medial cheek defects		
Dorsal nasal rotation flap	Special type of rotation flap; long sweeping arc that involves rotation of entire nasal dorsum (elevated at level of perichondrium or periosteum)	 outline
Bilateral advancement rotational flap (O-Z flap)	Bilateral rotation flap converting circular defect into a Z-shaped incision line, most useful on scalp (can be purely rotational or advancement with rotation)	 outline
<b>Transposition flap</b>		
Most complex design, redirects wound closure tension, moves tissue from area of surplus to area of need by <b>transpositioning across intervening islands of unaffected tissue</b>		
Rhomboid transposition flap	Rhomboidal-shaped flap created adjacent to round or oval defect and transposed into defect	 outline
Bilobed transposition flap	Recruits tissue from proximal nasal dorsum (more laxity) and transfers to defect, useful on distal nose	 outline
Nasolabial transposition flap	Flap from medial cheek adjacent to melolabial fold transposed to alar wound, useful in lateral and central alar wounds	 outline
Z-plasty	Useful for scars crossing relaxed tension lines or releasing contractures (redistributes tension over wound)	 outline
Paramedian forehead flap	2 stage flap for repair of subtotal to total nasal defects; forehead flap designed vertically to preserve supratrochlear artery supply; flap rotated 180° and sutured into nasal defect; 2-3 weeks later pedicle divided and repositioned	<b>Axial pattern flap as well</b>

**Split-Thickness Skin Graft (STSG)**

- Epidermis + partial-thickness dermis
- STSGs are categorized further as thin (0.005-0.012 in), intermediate (0.012-0.018 in), or thick (0.018-0.030 in) based on the thickness of dermis
- Advantages: ability to cover large defects (especially if graft fenestrated), higher likelihood of survival as less metabolic demand, allows for detection of tumor recurrence in cutaneous oncology

Thin STSG: 0.005–0.012 in  
Medium STSG: 0.012–0.018 in  
Thick STSG: 0.018–0.030 in

- Disadvantages: less cosmetically desirable color and texture, granulation tissue at donor site, increased contracture at wound site (more than with FTSG), lack adnexal structures (do not produce sebum, hair, sweat)
- Donor sites: buttocks, thighs, arms, abdomen
- One week postop: pink to skin-colored

### Composite Graft

- Epidermis + dermis + one more component (typically cartilage)
- Advantages: ability to restore missing cartilage in primary defect, maintains proper tissue architecture and function
- Disadvantages: highest metabolic demand (thus, highest likelihood of failure), size limited (due to blood supply)
- Donor sites: helix of ear, conchal bowl
- Most commonly used in nose (commonly nasal ala → cartilage restores proper function and prevents alar collapse during inspiration), and donor site often helical crus of ear

### Stages of Graft Survival (Table 6-8)

- Skin graft must re-establish blood supply at recipient sites
- Three stages: imbibition, inosculation, neovascularization

**Table 6-8 Stages of Skin Graft Survival**

Stages	Description
<b>1. <u>Imbibition</u></b>	First 24–48 h (ischemic period) Graft sustained by plasma exudate from wound bed Fibrin attaches graft to new bed Graft becomes edematous, ↑ weight by up to 40%
<b>2. <u>Inosculation</u></b>	Begins 48–72 h, lasts up to 7–10 days (graft vessels anastomose) Revascularization linking dermal vessels in graft to recipient bed Rationale for delayed grafting over sites devoid of perichondrium or periosteum (allows formation of granulation tissue with ↑ survival rate)
<b>3. <u>Neovascularization</u></b>	Occurs temporally with inosculation Capillary ingrowth from recipient wound base and sidewalls to graft If optimal conditions, full circulation reestablished within 4–7 days
<b>4. <u>Maturation</u></b>	Occurs months later Reinnervation of graft typically within 2 months of graft but may not be complete for months to years (full sensation may never fully return)

## 6.3 SURGICAL COMPLICATIONS

### Hematoma

- Risk of bleeding greatest in first 48 h (especially in immediate postoperative period)
- Provides medium for bacteria, prevents wound healing, ↑ wound tension (± dehiscence)
- Two types of hematoma: stable and expanding
- Stable hematoma
  - Non-expanding ecchymotic firm to fluctuant mass with sensation of pressure
  - Small, stable, non-infected, and not compromising tissue viability → no surgical intervention necessary (observation w/ warm compresses to hasten resorption)



- Expanding hematoma (Figure 6.5)
  - Enlarging ecchymotic fluctuant to firm mass with new onset pain (often throbbing)
  - Medical emergency if expanding hematoma in periorbital or cervical locations
- If very early hematoma (warm, swollen, fluctuant) → intervention recommended to prevent further progression (same intervention as for expanding hematoma)
- If late hematoma (liquefactive stage, 7–10 days after formation) → may aspirate w/ needle

## Wound Dehiscence

- Separation of previously apposed wound edges due to infection, hematoma, trauma, or wound tension; wounds may be re-sutured in cases of early dehiscence due to premature suture removal or trauma without infection; devitalized tissue may need to be removed

## Skin Necrosis

- Necrosis due to inadequate arterial supply and/or excessive tension; infection, hematoma, or dehiscence also results in decreased local circulation and subsequent necrosis if not treated properly
- May initially see pallor or cyanosis followed by dark brown-black color with hard eschar
- Treat conservatively; do not debride early necrosis (without evidence of infection or hematoma) as the superficial eschar will act as biological dressing

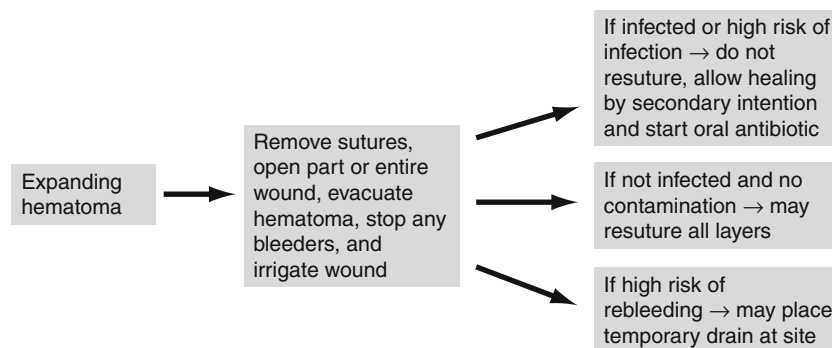
Porcelain white grafts portends poor prognosis for graft survival

## Infection

- Purulent exudate, cellulitis, lymphangitis, and fever may be present; if fluctuant with edema and purulent exudate, wound may need to be opened, irrigated and packed with iodoform gauze
- Perform bacterial culture; use topical or systemic antibiotics as needed

## Chondritis

- Occurs in surgery involving the ear; *Pseudomonas aeruginosa* commonly implicated in postoperative ear infections; treat with oral antibiotic with pseudomonal coverage



**Figure 6.5**  
Algorithm for expanding hematoma

## Suture Reaction

- Suture granuloma
  - Presents 1–3 months after surgery as an erythematous papule or sterile pustule along epidermal suture lines; ↑ risk of granuloma formation with larger caliber suture (more reactivity), braided sutures (vs. monofilament), and/or placement of too many knots
  - May resolve spontaneously; may treat with IL kenalog or lancing papule with subsequent suture removal
- Suture spitting
  - Results from subcutaneous sutures being too high in the dermis, can occur from several weeks to several months after surgery
- Suture track marks
  - Sutures too tight or left in place too long; puncture scars on either side of wound connected by linear suture lines give “railroad track” appearance

## Excessive Granulation Tissue

- Beefy red, friable appearance; occurs mainly in wounds healing by secondary intention
- Granulation tissue inhibits wound healing (prevents fibroblast proliferation)
- Treatment: destruction of tissue with silver nitrate, cautery, curettage, or shave removal

## Trapdoor Phenomenon

- “Pincushion” appearance (elevation above surrounding skin surface) seen mainly in transposition flaps due to either excess subcutaneous fat in flap, an oversized flap, insufficient tissue undermining or insufficient flap contact with base of wound

## Contact Dermatitis

- From topical antibiotic or adhesive; presents with erythematous plaque, ± vesicles and pruritus

## Ectropion/Eclabium

- Ectropion occurs when scar retracts and pulls down lower eyelid margin causing eversion; results in dry, irritated eye with inability to close eye fully
- Eclabium is eversion of lip due to wound with excessive tension

## Surface Contour Irregularity

- Spread scars occur in areas with high tension, high use (shoulders, chest, back), infection, or dehiscence
- Depressed scars and trapdoor defects most common in sebaceous areas, especially nose
- Can treat irregular contour with dermabrasion or scar revision (typically ≥ 8 week postop)

## Hypertrophic Scar/Keloid

- More common on chest/back, darker skinned patients, and secondary intention wounds
- Hypertrophic scars: arise early within 4 weeks postop and can regress
- Keloids may arise months after surgery, do not regress and frequently recur
- Treatment with IL steroid injection, silicone gel sheeting, pulsed dye laser, or scar revision

## 6.4 CRYOSURGERY AND ELECTROSURGERY

### Cryosurgery

Boiling point for liquid nitrogen:  $-196^{\circ}\text{C}$

- Targeted tissue destruction via necrosis induced by subzero temperature with liquid nitrogen
- Direct cellular damage due to ice crystal formation:
  - Ice crystal formation begins in extracellular system  $\rightarrow$  water leaves the cell resulting in intracellular dehydration and cell membrane shrinkage
  - Crystallization then forms inside the cell with subsequent expansion and tearing of the cell membrane; ice crystals also result in damage to organelles
- Indirect damage: cold-induced damage to capillaries causing local ischemic necrosis
- Rapid freezing with slow thaw is desirable as this produces intracellular ice crystallization; repeat freeze/thaw cycle creates further cell damage
- Melanocytes and vascular tissue are very susceptible to cold temperatures

Cell/Lesion Type	Temperature for Destruction
Melanocyte	$-5^{\circ}\text{C}$
Keratinocyte	$-25^{\circ}\text{C}$
Benign lesion	$-20$ – $25^{\circ}\text{C}$
Malignant lesion	$-50^{\circ}\text{C}$

### Electrosurgery (Tables 6-9, 6-10)

- Use of high-frequency alternating current to create thermal tissue destruction (includes electrosection, electrocoagulation, electrofulguration, electrodesiccation)
  - Electrocautery often mistakenly interchanged with the term electrosurgery
    - Electrocautery involves direct current producing thermal energy (tissue in contact with heated wire)
    - No current passing through patient
    - Safe for patients with pacemakers
- Forms of electrosurgery
  - Electrocoagulation: lower voltage, higher amperage; bipolar current thermally damages relatively deep tissue with  $\uparrow$  tissue coagulation
  - Electrosection: lower voltage, higher amperage; current penetrates deeper with  $\uparrow$  tissue coagulation; minimal peripheral heat damage to surrounding tissue
  - Electrofulguration: electrode held away from tissue, electrical spark crosses gap between tissue/electrode and burns tissue superficially; high voltage, lower amperage
  - Electrodesiccation: electrode touches tissue causing superficial tissue dehydration (desiccation);  $\downarrow$  heat compared to electrosection; high voltage, low amperage; low energy limits tissue damage; best for superficial, avascular lesions (seborrheic keratosis)

**Table 6-9 Types of Electrosurgery**

Type of procedure	Voltage	Amperage	Skin contact w/ electrode	Circuit
<b>Electrosection</b>	$\downarrow$	$\uparrow$	Y	Biterminal
<b>Electrocoagulation</b>	$\downarrow$	$\uparrow$	Y	Biterminal
<b>Electrofulguration</b>	$\uparrow$	$\downarrow$	N	Monoterminal
<b>Electrodesiccation</b>	$\uparrow$	$\downarrow$	Y	Monoterminal

**Table 6-10 Electrosurgical Terminology**

Terms	Description
1. <b><u>Monopolar/Bipolar</u></b>	Misnomer since treatment electrodes without true positive/negative poles; instead, the terms monoterminal and biterminal should be used
2. <b><u>Monoterminal</u></b>	Only one electrode used to deliver current to the patient
3. <b><u>Biterminal</u></b>	Two electrodes used to deliver current to patient; current flows from one electrode to the other to complete an electrical circuit

## 6.5 PREOPERATIVE CONSIDERATIONS

### Risk Factors for Bleeding

- Certain medications, significant alcohol use, severe hypertension

Medications	Comment
<b>Aspirin</b>	Discontinue (if used for primary prevention and not medically indicated) 10–14 days prior to surgery
<b>NSAID</b>	Varies, may discontinue 2–3 days prior to surgery
<b>Warfarin</b>	Varies, most do not discontinue
<b>Clopidogrel</b> (Plavix)	Varies, most do not discontinue (can d/c 5 days before surgery)
<b>Others:</b> feverfew, garlic, ginkgo, ginger, ginseng, dong quai root, chondroitin, vitamin E, bilberry	

### Antibiotic Prophylaxis

- Antibiotic given 30–60 min prior to surgery
- Non-oral site: cephalexin 2 g (if PCN-allergic: clindamycin 600 mg or azithromycin 500 mg)
- Oral site: amoxicillin 2 g (if PCN-allergic use clindamycin 600 mg or azithromycin 500 mg)

NEED antibiotic prophylaxis	DO NOT need antibiotic prophylaxis
<b><u>High risk</u></b> Prosthetic cardiac valves History of previous bacterial endocarditis Complex cyanotic congenital heart disease (i.e., transposition of great vessels) Surgical systemic pulmonary shunts or conduits  <b><u>Moderate risk</u></b> Mitral valve prolapse (MVP) with valvular regurgitation and/or thickened leaflets Hypertrophic cardiomyopathy Acquired valve dysfunction (rheumatic heart disease) Certain other congenital cardiac malformations Orthopedic prosthesis ( <b>first 6 months</b> postop)	<b><u>Negligible risk per AHA</u></b> Isolated secundum atrial septal defect Ventricular septal defect Patent ductus arteriosus (without residua beyond 6 months) Physiologic “innocent” heart murmur  MVP without valvular regurgitation Cardiac pacemakers, cardiac stents, or implanted defibrillators, CABG Previous rheumatic fever (no valvular dysfunction)



**Table 6-11 Mohs Surgery Indications**

Indication	Description
<b>Location</b> (tissue sparing)	Eyelids, lips, ears, nose, digits, genitalia, nails, periorbital
<b>Tumors at high risk for recurrence or metastasis</b>	<div>Merkel cell carcinoma</div> <div>Morpheaform or infiltrative BCC</div> <div>Dermatofibrosarcoma protuberans</div> <div>Malignant fibrous histiocytoma</div> <div>Microcystic adnexal carcinoma</div> <div>Melanoma</div> <div>Sebaceous carcinoma</div> <div>Perineural BCC or SCC</div> <div>Atypical fibroxanthoma</div> <div>Angiosarcoma</div>
<b>Histopathologic findings</b>	<div>Aggressive histologic type (i.e., perineural invasion)</div> <div>Positive margin after simple excision</div>
<b>Clinical findings</b>	Recurrent tumor, large diameter tumors (>2 cm trunk, >1 cm on face), poorly defined clinical margins
<b>PMHx indication</b>	Skin previously treated with ionizing radiation

**Mohs Micrographic Surgery**

Scalpel oriented at 45° angle to skin in Mohs surgery

- Examines peripheral margins of fresh tissue via sectioning in horizontal planes; lesion must grow in contiguous fashion to be considered for Mohs surgery

**6.6 LOCAL ANESTHESIA**

Loss of sensation occurs in following order: temperature and pain (C-type fibers), touch, pressure, vibration, proprioception, motor function

**Anesthetics** (Tables 6-12, 6-13, 6-14)

- Mechanism of action: reversible nerve conduction blockage (interferes with influx of sodium ions into cell resulting in inability for depolarization); two types: amides and esters
- Three major components: connecting chain (ester or amide), amine portion, aromatic end
- Amides
  - Amides with two i's in the name
  - Metabolized by microsomal liver enzymes (cyt p450 3A4); excreted by kidneys
  - Risk factors for toxicity: severe liver disease, drugs that ↑ half-life (i.e., propranolol)
  - Cross-reactivity: amides do not have any derivatives of PABA (para-aminobenzoic acid), so ↓ cross-reactivity and sensitization compared to esters (but methylparabens may be used as preservative, which is metabolized to PABA by-product)
- Esters: cocaine, procaine, tetracaine, chlorprocaine
  - Cleared via hydrolysis by plasma pseudocholinesterase; excretion by kidneys
  - Do not use if pseudocholinesterase deficiency or hypersensitivity to PABA or derivatives
  - Allergic reaction typically due to PABA, an ester intermediate metabolite (may cross-react with paraphenylenediamine (PPD), para-aminosalicylic acid, sulfonamides, azo dyes, **other ester anesthetics**, benzocaine (topical), and PABA sunscreens)
- Tumescent anesthesia: large volumes of dilute lidocaine (0.05–0.1%) and epinephrine (1:1,000,000) to produce complete anesthesia and hemostasis; infuse over 90–120 min; peak plasma dose 4–14 h after infusion, lasts up to 24 h; max safe dose is **55 mg/kg**
- Digital blocks: use minimal anesthetic with epi, should not exceed 1.5 ml per side (3 ml total per finger)
- Topical anesthetics
  - EMLA: eutectic mixture of 2.5% lidocaine, 2.5% prilocaine, under occlusion
  - Ela-Max (LMX): 4 or 5% lidocaine, no occlusion necessary

Do not use in infants as it can cause methemoglobinemia

## Epinephrine

- Prolongs anesthesia and decreases anesthetic's risk for systemic toxicity by ↓ absorption
- Caution in ischemic heart disease, severe HTN, pheochromocytoma, narrow-angle glaucoma, uncontrolled hyperthyroidism, drugs (β-blockers, MAOI, TCAs), pregnancy

**Table 6-12 Anesthetic Properties**

Property	Factor	Description
Onset of action	<b>pKa level</b>	↓ pKa → more rapid onset (closer to 7.4 means more uncharged base form, which can pass through neuronal cell membrane)
Duration of action	<b>Protein binding</b>	↑ Ability of binding plasma proteins → increased duration of action (lipid solubility less important)
Potency	<b>Lipid solubility</b>	↑ Lipid solubility → ↑ potency (↑ penetration of hydrophobic environment)

**Table 6-13 Ester and Amide Anesthetics**

Drug Name	Potency	Onset	Duration	Important Features
<b>AMIDES</b>				
<b>Prilocaine</b>	++	Rapid	+	Shortest acting; risk of <b>methemoglobinemia</b> (risk ↑ with infants and G6PD deficiency)
<b>Lidocaine</b>	++	Rapid	++ (1–6 h)	Adult max dose: <b>4.5 mg/kg</b> without epi; <b>7.0 mg/kg (500 mg)</b> w/ epi 1:100,000 epinephrine
1% lidocaine = 10 mg/ml: for 70 kg person give 50 ml or 500 mg max			Class B pregnancy	Pediatric max dose: 3–4 mg/kg with epi
<b>Mepivacaine</b>	++		++	
<b>Etidocaine</b>	++++	Rapid	+++	
<b>Bupivacaine</b>	++++	Slow	++++ (3–7 h)	<b>Longest acting; ↑ cardiac arrhythmias</b>
<b>ESTERS</b>				
<b>Procaine</b>	+		+	(30 min)
<b>Chlorprocaine</b>	+	Rapid	+	pKa high but fast onset due to ↑ concentration
<b>Tetracaine</b>	++++	Slow	+++	Cocaine vasoconstrictive ester; others vasodilating

**Table 6-14 Reactions to Anesthetics**

Dose	Symptoms	Management
<b>Lidocaine Overdose</b>		
1–6 µg/ml	<b>Paresthesias</b> (circumoral, tongue, digital), euphoria, lightheadedness, restlessness, talkativeness, <b>metallic taste</b>	Observation
6–9 µg/ml	Nausea, vomiting, tremors, blurred vision, <b>tinnitus</b> , muscle twitching, confusion, excitement, psychosis, <b>slurred speech</b>	Maintain airway, ± diazepam
9–12 µg/ml	<b>Seizures</b> and cardiopulmonary depression	Respiratory support
>12 µg/ml	Coma, cardiopulmonary arrest	CPR, life support
<b>Vasovagal Reaction</b>		
Excess parasympathetic tone (↓ pulse, ↓ BP): diaphoresis, nausea, vagal-induced bradycardia, and hypotension Most common side effect seen		Cold compresses, Trendelenburg
<b>Epinephrine Reaction</b>		
Self limited: palpitations, ↑ pulse, ↑ BP, anxiety, diaphoresis, tremor, HA Serious effects (rare): cardiac arrhythmias, cardiac arrest		Monitor pulse/BP, short-lived typically
<b>Anaphylactic Reaction</b>		
(↑ Pulse, ↓ BP): tachycardia, angioedema, stridor, bronchospasm		SubQ epinephrine, maintain airway

## 6.7 SUTURES, ANTISEPTICS, AND DRESSINGS

**Table 6-15 Physical Characteristics of Suture Material**

Physical Characteristic	Definition	Comment
<b>Coefficient of friction (COF)</b>	Ease with which suture will pull through tissue	Polypropylene slides easily (↓ COF) Knot strength directly proportional to COF (↑ knot strength with ↑ COF)
<b>Suture configuration</b>	<b>Monofilament</b> – single strand (nylon or polypropylene)	↓ Coefficient of friction (COF) so slides easily through tissue causing less trauma
	<b>Multifilament</b> – made of several strands either twisted or braided	Handle/tie more easily, ↑ tensile strength, but ↑ COF, ↑ risk <b>infection</b> (organisms may be harbored between filaments)
<b>Capillarity</b>	Ability of suture to absorb and transfer fluid	Multifilament has ↑ capillarity, which also increases risk of harboring bacteria
<b>USP size</b>	Diameter of suture material	Related to tensile strength (smaller the number, greater tensile strength/diameter)
	Choose smallest suture providing adequate tensile repair	
<b>Elasticity</b>	Ability of suture to regain former shape (original size/shape) after being stretched	↑ Elasticity means suture can stretch with tissue and will recoil when swelling subsides
<b>Knot strength</b>	Security of tied knot and degree of slippage occurring in a knot	Polyglycolic acid has one of highest knot strengths
<b>Memory</b>	Suture's tendency to retain natural configuration after deformation (determined by elasticity and plasticity of material)	High memory sutures like polypropylene and nylon have greater tendency to untie themselves (do not handle easily, lower knot strength requiring greater number of ties); silk w/ ↓ memory (rarely unties)
<b>Plasticity</b>	Ability of suture to retain new length and form after being stretched	Important in tissue edema – as sutures with plasticity (polypropylene) will accommodate edema without cutting into tissue; ↑ plasticity may lead to ↑ knot security
<b>Pliability</b>	How easily suture can be bent	Braided suture (silk) most pliable
<b>Tensile strength</b>	Force required to snap the suture (determined by diameter and composition of suture)	Larger sutures usually have more tensile strength; synthetic material usually stronger than natural materials like silk
<b>Tissue reactivity</b>	Degree of inflammation elicited by placement of suture in wound (degree of foreign body reaction)	Natural suture w/ ↑ inflammatory response vs. synthetic materials (nylon); ↑ suture diameter w/ ↑ tissue reaction; ↓ reactivity with monofilament (unlike multifilament)
<b>Absorption</b>	Absorbable sutures lose tensile strength over time by absorption	<b>Proteolysis</b> – natural materials (cat gut or silk) <b>Hydrolysis</b> – synthetic absorbable sutures

**Table 6-16 Absorbable Sutures**

Suture	Structure	Tensile Strength	Absorption Complete	Knot Security	Handling	Tissue Reactivity	Comments
<b>Plain gut</b>	Multifilament Twisted	Low	60–70 days	Poor	Poor	High	
<b>Chromic gut</b>	Multifilament Twisted	Low	80 days	Poor	Poor	High	
<b>Polyglycolic acid</b> (Dexon)	Multifilament Braided	Good 30% @ 3 wks	90 days	Good	Good	Low	
<b>Polyglactin 910</b> (Vicryl)	Multifilament Braided	High 50% @ 3 wks	90 days	Good	Good	Low	
			Copolymer of glycolide + L-lactide				
<b>Polydioxanone</b> (PDS)	Monofilament	<b>High</b> 50% @ 4 wks	<b>180 days</b>	Poor	Poor	Low	<b>High tension areas</b>
<b>Glycolic acid</b> (Maxon)	Monofilament	High 60% @ 4 wks	180 days	Good	Good	Low	High tension areas
			Polytrimethylene carbonate				
<b>Poliglecaprone 25</b> (Monocryl)	Monofilament	High 70% @ 1 wks, 30% by 2 wks	90–120 days	Good	Good	Low	<b>Highest initial tensile strength</b>
			Highest initial knot security and tensile strength				
<b>Glycomer 631</b> (Biosyn)	Monofilament	Good 40% @ 3 wks	90–110 days	Poor	Good	Low	High tension areas

**Table 6-17 Nonabsorbable Sutures**

Suture	Configuration	Tensile Strength	Memory	Knot Security	Handling	Tissue Reactivity	Comments
<b>Silk</b> (natural suture)	Braided	Low	Low	Good to excellent	Excellent	High	Used in mucosa and body folds
	↑ Capillarity = ↑ infection risk; soft/pliable suture						
<b>Nylon</b> (Ethilon)	Monofilament	High	High	Poor	Poor	Low	
<b>Nylon</b> (Surgilon)	Multifilament, braided	High	Good to high	Fair	Good	Low	
<b>Polypropylene</b> (Prolene)	Monofilament	Moderate	High	Poor	Good	Least	Running subcuticular sutures
			↓ COF: decreased resistance in tissue				
<b>Polyester</b> (Ethibond)	Braided	Very high	Good	Good	Good	Low	Mucosal surfaces
<b>Polybutester</b> (Novafil)	Monofilament	High	Low	Fair to Good	Good	Low	



## Needles

- Most common 3/8 circle, triangular-shaped needle point; needle composed of three parts: tip, body and shank (latter where suture material attached); needle driver grasps body of needle
- Reverse cutting needles have advantage of minimizing risk of tearing through wound edge during suture placement
- Surgical yield of needle: amount of angular deformation occurring before permanent deformation of needle
- Ultimate moment of needle: measure of maximum strength by bending needle to 90°
- Types of needles (per one manufacturer): Ethicon P (plastic), PS (plastic skin), PC (precision cosmetic), and FS (for skin)

## Antiseptics (Table 6-18)

- Know disadvantages

**Table 6-18 Antiseptics**

Name	Spectrum	Advantages	Disadvantages
<b>Chlorhexidine</b> (Hibiclens)	Broad antimicrobial spectrum (bacterial, viral, fungal)	Rapid onset, sustained activity, additive effect w/ repeated use, ↓ skin absorption	Ocular irritation and <b>ototoxicity</b>
<b>Hexa-chlorophene</b> (pHisoHex)	Gram + cocci	Sustained activity	<b>Teratogenic</b> ; skin absorption can cause <b>neurotoxic</b> effects
<b>Povidone-Iodine</b> (Betadine)	Broad antimicrobial spectrum including fungi	Fast acting  May cross-react with radiopaque iodine or iodides in medications	Skin irritant, <b>contact dermatitis</b> , effective only if <b>dry</b> ; skin/fabric staining, <b>inactivated by blood or sputum</b> , ↓ duration of action
<b>Benzalkonium</b> (Zephiran)	Gram + bacteria Gram – bacteria  Quaternary ammonium (cationic) detergent	Not irritating to tissue; stable, strong antimicrobial action	Slow onset, no sustained activity, inactivated by anionic compounds such as soap
<b>Isopropyl Alcohol</b>	Gram + bacteria	Inexpensive	<b>Flammable</b> in setting of cautery; skin irritant
<b>Silver Sulfadiazine</b> (Silvadene)	Broad spectrum  In addition to sulfonamide component, silver interacts with bacterial cell wall and membrane	Broad coverage	Contraindicated if sulfonamide hypersensitivity; argyria (local), leukopenia; caution if renal or liver disease or G6PD deficiency
<b>Hydrogen Peroxide</b>	Bacteria, fungi (at ↑ H <sub>2</sub> O <sub>2</sub> concentration)	Rapid onset	Corrosive to normal skin, bleaching action

**Dressings (Table 6-19)**

- Wound dressing substitute for native epithelium; ideally dressing should maintain moist environment at wound interface, remove excess exudate, provide mechanical protection and hemostasis, serve as barrier to microorganisms, provide gaseous exchange but prevent leakage, be nonadherent with easy removal
- Wounds: if scab thick, slower process of reepithelialization; fluid from occluded wounds contains many endogenous wound healing factors; low oxygen requirement for optimal fibroblast proliferation (hypoxia increases angiogenesis)
- Least to most absorbent (in order): films, hydrocolloids, hydrogels, foams, alginates

**Table 6-19 Dressings**

Dressing	Structure	Uses	Advantages	Disadvantages
<b>Films</b> (Tegaderm, Opsite)	Polyurethane semipermeable transparent thin sheet	IV sites, superficial burns, wounds with minimal exudate	Transparent, permeable to H <sub>2</sub> O vapor, ↑ reepithelialization, barrier to bacteria, ↓ pain	May adhere to wound No absorption of wound drainage
<b>Hydrocolloids</b> (Duoderm, NuDerm)	Semipermeable opaque sheet of starch, gelatin, elastomer, pectin, adhesive (turns into gel when exudate absorbed)	Chronic ulcers, burns, surgery wounds	Adherent (occlusive), absorbs drainage, debrides wound, ↑ granulation tissue in open wounds, creates bacterial and physical barrier, stays on wound several days	Opaque, expensive, trauma with dressing changes, may stimulate excess granulation tissue
<b>Hydrogels</b> (NuGel, 2nd Skin, Vigilon)	Hydrophilic semipermeable semitransparent polymer gel	Ulcers, thermal burns, painful wounds, laser resurfacing, graft donor sites, mild-moderately exudative sites	Semi-transparent, highly absorbent, hydrating, ↓ pain, no adherence to wound	Frequent dressing changes, requires secondary dressing
<b>Foams</b> (Hydrasorb, Vigifoam, Synthoderm, Flexzan)	Polyurethane semipermeable opaque sponge-like foam	Wounds with moderate exudate, burns, Mohs defects	Permeable to H <sub>2</sub> O vapor, conforms to wound shape, absorbent	Opaque, drying effect, requires secondary dressing (not adherent)
<b>Alginates</b> (Sorbsan, Algisorb, Seasorb)	Composed of calcium alginate (seaweed component)	<b>Highly exudative wounds</b> , full-thickness burns, STSG, Mohs defects	Highly absorbent, hemostatic, no adherence to wound, infrequent dressing change	Requires secondary dressing, may have unpleasant odor

**6.8 NAIL SURGERY****Nail Surgery**

- Important points (see Chapter 1 for nail anatomy) listed below
- Nail matrix
  - Proximal nail matrix forms superficial (dorsal) surface of nail plate
  - Distal nail matrix forms deep (ventral) surface of nail plate; lunula is distal 1/3 matrix
  - Distal matrix surgery better for nail appearance than proximal matrix surgery as defect of nail plate less noticeable on undersurface of nail plate
- Nail bed
  - Surgery of nail bed rarely causes permanent nail plate dystrophy but may cause mild onycholysis
  - Nail bed: no subcutaneous tissue underneath it (dermis sits directly on periosteum)

- Anesthesia
  - Inject either as digital block and/or wing block
  - Digital block: 2% plain lidocaine, superficial with volume <1–1.5 ml on each side of digit (total 3 ml per digit)
- Useful procedures: punch biopsy ( $\pm$  prior nail avulsion), lateral longitudinal excision, elliptical excision in nail bed or nail matrix
- Biopsy
  - Procedures should be oriented properly for healing to be optimal with minimal scarring
    - Matrix: biopsy along horizontal axis
    - Nail bed: biopsy along vertical or longitudinal axis
  - Biopsies should be taken down to level of periosteum (undermine at same level)
  - Preferable for excision to be  $\leq 3$  mm; suture if possible, but  $\leq 3$  mm does not need suture
  - When biopsing pigmented band, specimen must be taken from nail matrix, where pigment generated (matrix exploration); matrix w/ highest risk of scarring so choose distal matrix if possible; unusually melanoma can start in nail bed and spread to matrix
- Excision
  - Elliptical excision should be in horizontal direction in matrix and vertical in nail bed
  - Nail matrix excision/repair results in thinner nail plate due to the fact that nail plate thickness is proportional to length of matrix
- Avulsion
  - Nail avulsion can be partial or total and may be performed either distally or proximally
  - Procedure allows for exploration of nail bed and matrix for tumors and subsequent biopsy if needed
  - Distal technique: Freer septum elevator used to loosen nail plate from attachment to nail bed, matrix, proximal and lateral nail folds by inserting into hyponychium toward the matrix
  - Proximal technique: Freer septum elevator inserted at the proximal nail fold
  - Partial nail avulsion: often used in longitudinal melanonychia involving lateral  $\frac{1}{4}$  nail plate or if patient with ingrown toenail

## 6.9 COSMETIC DERMATOLOGY

Do not resurface if patient with recent (6–12 months) isotretinoin use since medication causes atrophy of the pilosebaceous unit, which is where reepithelialization after peel originates from  $\rightarrow$  so possible impaired wound healing with  $\uparrow$  scar formation

### Chemical Peels (Table 6-20)

- Application of chemical to skin to produce a controlled partial-thickness injury with subsequent epidermal and varying dermal repair; degree of clinical improvement directly proportional to depth of peel
- Antiviral prophylaxis given for medium-depth and deep peels
- Frost: intensity correlates with level of peel
  - Level 1: irregular light frost (erythema w/ streaky frosting); superficial epidermis
  - Level 2: uniform white frost with underlying erythema; level of upper dermis
  - Level 3: solid white enamel frosting; level of reticular dermis
- Classified as superficial, medium, and deep peels (see Table 6-20)
- Superficial peels
  - Injury limited to epidermis only
  - Glycolic acid: needs to be neutralized with sodium bicarbonate
  - Jessner's solution, TCA, and salicylic acid do not need neutralization
  - Salicylic acid: keratolytic and comedolytic
- Medium depth peels
  - Injury at or through level of papillary dermis
  - Indications: epidermal growths (AK, SK, lentigines), dyschromia, rhytides

**Table 6-20 Chemical Peels**

Terms	Description
<b>1. Superficial: very light</b>	Trichloroacetic acid (TCA) 10–20% Salicylic acid Alpha-hydroxy acids Tretinoin solution
<b>2. Superficial: light</b>	Jessner's solution: salicylic acid/lactic acid/resorcinol/ethanol TCA 25–30% Glycolic acid 70%
<b>2. Medium</b>	35–40% TCA 70% glycolic acid + 35% TCA Jessner's solution + 35% TCA 88% phenol (rarely used)
<b>3. Deep</b>	Baker Gordon phenol TCA > 50%

- Deep peels
  - Injury at depth of reticular dermis
  - Phenol: keratocoagulant, only deep chemical peeling agent (must use IV sedation with full face procedure), known to be cardiotoxic (do not exceed procedure time over 60–90 min and need cardiac monitoring), hepatotoxic, nephrotoxic
  - Baker formula most widely used deep peeling agent: phenol, distilled water, croton oil, liquid hexachlorophene
  - Complications: prolonged erythema (most common with phenol), scarring, permanent hypopigmentation, hyperpigmentation, scarring, milia, acne

### Botulinum Toxin (BTX) (Table 6-21)

- Purified protein toxin produced from *Clostridium botulinum*; seven serotypes which differ slightly in clinical effect and mechanism of action, but all block neuromuscular transmission causing temporary paralysis of striated muscle
- BTX specifically inhibits acetylcholine (ACh) release by cleaving proteins in the SNARE complex (required for ACh release)
  - BTX type A light chain cleaves SNAP25 (synaptosome-associated protein), key protein for successful docking and release of ACh from vesicles within nerve endings
  - BTX type B light chain cleaves synaptobrevin or VAMP (vesicle-associated membrane protein)
- BOTOX (type A): FDA-approved for glabellar rhytides and hyperhidrosis; each vial contains 50 or 100 units of vacuum-dried BTX A neurotoxin; smaller volume with higher dose keeps delivery precise with little diffusion
- Instructions recommend reconstitution with sterile, non-preserved saline, but preserved saline results in less pain on injection and does not reduce stability of toxin
- Contraindication: any neuromuscular disorder, infection/inflammation at injection site, known hypersensitivity to product or any of the contents, pregnancy (category C - safety for use during pregnancy has not been established) or breastfeeding
- Most effective in reducing dynamic facial lines (vs. static lines) (Table 6-21)
- Glabellar rhytides (procerus, corrugator supercilii):
  - Stay 1 cm above orbital rim
  - If BTX diffuses to levator palpebrae muscle, eyelid ptosis may occur
- Horizontal forehead lines (frontalis muscle):
  - If weaken frontalis muscle significantly but eyebrow depressors not weakened concomitantly, will have unopposed action of depressors with lowering of the brow and an angry expression
  - If patient narrow brow (<12 cm) between temporal fusion lines at mid brow level, receive fewer injection site (four instead of five)
- Crow's feet (orbicularis oculi):
  - Weakening of orbicularis oculi muscle by three injection sites
  - Do not inject while patient is still smiling as toxin may affect ipsilateral zygomaticus complex, causing ptosis of upper lip



- Perioral rhytides (orbicularis oris):
  - Vertical lines radiating outward from vermilion border due to overactive orbicularis oris
  - Goal to produce mild weakening of muscle (avoiding paresis, which would interfere with speech); small doses 1–2 units per lip quadrant sufficient (total eight injection sites)
- Bunny lines (nasalis):
  - Inject anterior to nasofacial groove on lateral wall of nose to soften ‘bunny lines’ (radial lines fanning obliquely across radix of nose); inject superficial to angular vein
  - Avoid injecting nasofacial groove as this can affect levator labii superioris and levator superior alaeque nasi
- Depressor anguli oris (DAO):
  - Contraction causes downward turn of corner of mouth, creating negative facial expression
  - Inject 3–5 units at level of mandible (posterior margin), close to anterior margin of masseter; complications include asymmetric smile and flaccid cheek
  - Patients using perioral muscles intensely are not good candidates for DAO injections
- Complications:
  - Brow ptosis may occur while glabellar complex being treated if BTX inadvertently affects frontalis muscle; may also occur if frontalis muscle being treated in patient with already low-set eyebrows
  - Quizzical appearance may appear when horizontal forehead lines are treated without treatment of most lateral frontalis fibers, which results in upward pull from the nontreated fibers
  - Upper eyelid ptosis occurs typically with treatment of glabellar complex; toxin diffuses through orbital septum affecting upper eyelid levator muscle; appears as early as 48 h and as late as 14 days after treatment, lasts 2–12 weeks; avoid complication by injecting small volume with high concentration and always inject 1 cm above orbital rim; can treat with apraclonidine 0.5% eye drops, which is an  $\alpha$ -adrenergic agonist and may lift lid by 1–2 mm (compensates for weakness of levator palpebrae superioris by causing Muller’s muscle to contract)

### Soft Tissue Augmentation (see Table 6-22)

- Used for augmentation of soft tissue (i.e., lips, nasolabial folds) and wrinkles
- Injectable fillers may be composed of hyaluronic acid, collagen, fat, calcium hydroxylapatite
- Side effects/complications include but not limited to bruising, granuloma formation, hematoma and infection

### Hair Restoration

- Hair transplant (follicular unit transplantation) occurs with relocation of hair via follicular units, which are naturally occurring groupings in the scalp; several grafts needed
  - Follicular units: composed of 1–4 terminal hairs, 1–2 vellus hairs with the associated glands, arrector pili, and adventitial collagen
  - Once strip of donor tissue removed, follicular units are taken out intact through careful stereomicroscopic dissection
  - Follicular unit density during hair restoration is typically  $>30$  follicular units/cm<sup>2</sup>
- FDA-approved medical treatments for male-pattern alopecia include topical minoxidil and finasteride (Propecia); latter is a type II  $5\alpha$ -reductase inhibitor and leads to decreased conversion of testosterone to dihydrotestosterone (DHT); side effects of finasteride include decreased libido, gynecomastia, decreased prostate-specific antigen (PSA) level

**Table 6-21 Muscles Treated with BTX**

Muscle	Resulting Rhytides	Comments
<b>Nasalis</b>	Bunny lines (radial lines across radix of nose)	Avoid angular vein
<b>Orbicularis oculi</b>	Crow’s feet (horizontal to oblique lines radiating from lateral canthus)	
<b>Frontalis muscle</b>	Horizontal forehead lines	Complications: quizzical appearance, brow ptosis
<b>Procerus, corrugator supercilii</b>	Glabellar lines	Complications: eyelid ptosis, brow ptosis (latter rare)

Three to five percent of the population have an allergy to bovine collagen

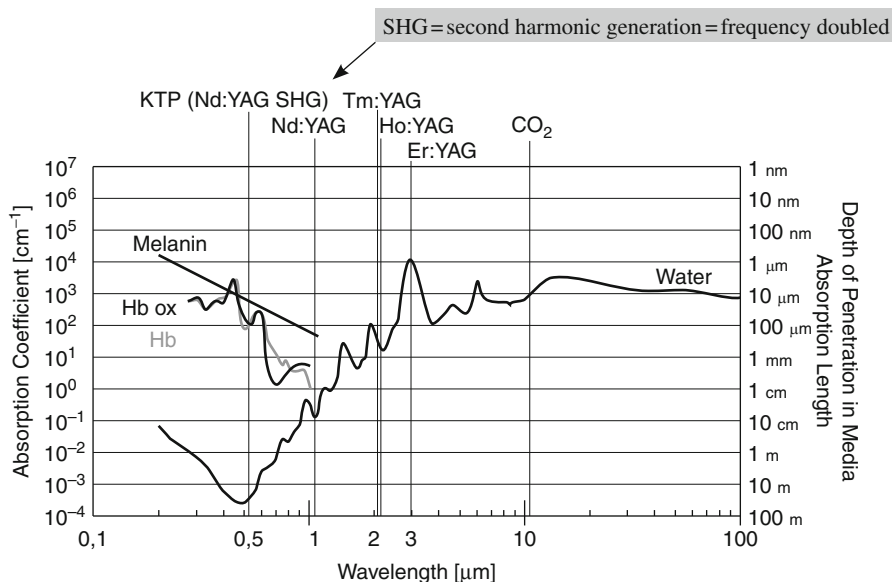
**Table 6-22 Injectable Fillers**

Name	Composition	Duration (months)	Level of implantation	Comments
<b>Cosmoderm I</b>	Human collagen + plain lidocaine	3–4 months	Superficial to mid-dermis	No pretesting, from <b>neonatal foreskin</b>
<b>Zyderm I</b>	Bovine collagen + lidocaine	3–4 months	Superficial to mid-dermis	+ Pretesting (two tests 2–4 weeks apart)
<b>Autologen</b>	Human collagen (from pt's own skin)	4–9 months	Mid-dermis	No pretesting
<b>Hylaform</b>	Hyaluronic acid (from <b>rooster comb</b> )	3–6 months	Mid-dermis	No pretesting
<b>Restylane</b>	Hyaluronic acid (from <b>bacterial fermentation</b> )	4–6 months	Mid-dermis	No pretesting
<b>Zyderm II</b>	Bovine collagen + plain lidocaine	3–6 months	Mid-dermis	+ Pretesting
<b>Artecoll</b>	Polymethylmethacrylate beads in bovine collagen suspension	Permanent	Deep dermis	+ Pretesting
<b>Cosmoplast</b>	Human collagen cross-linked w/ glutaraldehyde + plain lidocaine	3–4	Deep dermis	
<b>Hyaloform plus</b>	Hyaluronic acid (rooster comb)	3–6	Deep dermis	
<b>Perlane</b>	Hyaluronic acid ( <b>bacterial fermentation</b> )	3–9	Deep dermis	
<b>Zyplast</b>	Bovine collagen cross-linked w/ glutaraldehyde + plain lidocaine	3–5	Deep dermis	+ Pretesting
<b>Isolagen</b>	Cultured autologous human fibroblasts	Unclear	Versatile	
<b>Juvederm</b>	Hyaluronic acid	3–6	Dermis (level varies if ultra or plus)	
<b>Radiesse</b>	Calcium hydroxylapatite microspheres in polysaccharide gel	9 months–5 years	Subdermal	Can be seen on x-ray
<b>New-Fill, Sculptra</b>	Poly-L-lactic acid	24	Subdermal	FDA-approved for <b>HIV-associated lipoatrophy</b>
<b>Alloderm</b>	Acellular human cadaveric dermis	3–6	Subdermal implant	
<b>Autologous graft</b>	Fat harvested from patient	6–24		

## Lasers (Light Amplification by Stimulated Emission of Radiation) (Tables 6-23, 6-24, 6-25, 6-26)

- Laser light: monochromatic (single, discrete wavelength), spatially coherent (light in phase), collimated (light in parallel fashion)
- Laser treatment based on principle of selective thermolysis: targeted lesion may be destroyed by chromophore absorption of laser light without significant thermal damage to surrounding normal tissue; pulse duration (exposure time) must be equal to or shorter than the target's thermal relaxation time (TRT, cooling time or time for target to lose 50% heat) to confine thermal damage
- Thermal damage time (TDT): time required to irreversibly damage target with sparing of surrounding tissue; pulse duration  $\leq$  TDT allows for efficacy with  $\downarrow$  epidermal damage
- Depth of penetration directly proportional to wavelength (i.e., Nd:Yag 1064 nm penetrates deeper than PDL 585 nm);  $\uparrow$  scattering with decreasing  $\lambda$  (scattering mostly due to collagen)
- Chromophores: components in skin which absorb laser light
  - Endogenous: hemoglobin, melanin, water; exogenous: tattoo ink
- Laser characteristics: wavelength, pulse duration, spot size, fluence ( $\text{J}/\text{cm}^2$ ), power ( $\text{J}/\text{s}$ )
- **Gain medium** determines wavelength of light: liquid (dye lasers), gas (argon,  $\text{CO}_2$ , helium-neon), solid (Nd:Yag, ruby)
- **Pulse duration** (exposure time of laser):
  - Determines confinement of heat and extent of thermal injury in tissue
  - Best if pulse duration  $\leq$  TRT
- **Spot size**: Larger spot size allows for deeper energy penetration (less scattering)
- **Cooling**: different types of epidermal cooling to minimize epidermal damage: passive (aqueous gel), active contact cooling (water encased in sapphire or glass housing), dynamic active cooling (cryogen spray), forced air cooling
- Q-switched or "quality-switched": allows accumulation of excessive energy in laser cavity prior to emission; extremely short pulses of very high power (nanosecond range); used mainly for removal of tattoo pigment and superficial pigmented lesions
- Hair removal:
  - Target thought to be bulge of hair follicle as well as dermal papilla
  - Best when pulse duration  $\leq$  TRT of hair follicle (40–100 ms for terminal hairs) and  $\geq$  TRT of epidermis (3–10 ms) to minimize epidermal damage; thus, optimum pulse duration 10–50 ms; use shorter wavelength laser (ruby) for blond, white, red, and gray hairs since better absorption of melanin
- Pigmented lesions (epidermal pigment):
  - Use QS lasers ( $\downarrow\downarrow$  pulse duration): QS KTP, QS ruby, QS Nd:Yag (532 nm)
  - Target endpoint: uniform but faint whitening, no epidermal disruption (higher fluences will have solid whitening w/ epidermal disruption and pinpoint bleeding)

TRT: proportional to square of target's diameter (so shortest TRT in chromophore with smallest size)



**Figure 6.6**

### Chromophore absorption spectrum

(Reprint from Teichman O, Herrmann T, Bach T. Technical aspects of lasers in urology. World Journal of Urology. June 2007; 25(3); 221–225)

- Tattoos:
  - QS lasers used to remove tattoo pigment; of note, white/peach/pink/flesh-toned tattoo color may turn dark gray immediately after treatment with QS laser (reduction of ferric oxide to ferrous oxide)
  - Amateur tattoo: usually clears after 3–5 treatments with QS laser
  - Professional tattoo: may require ten or more treatments (dense pigment)

**Table 6-23 Chromophores**

Chromophore	Absorption Peaks	Laser
<b>Hemoglobin</b>	418 nm, 542 nm, 577 nm	Argon, copper vapor, KTP, pulsed dye
<b>Melanosome</b>	300–1000 nm (peak 335 nm)	PDL, KTP, ruby, alexandrite, diode, Nd:Yag
<b>Water</b>	1450 nm, 1950 nm, 3000 nm	CO <sub>2</sub> , erbium, diode (1450 nm), Nd:Yag (1320 nm)

↑ Absorption of melanin at lower  $\lambda$  (300–600 nm) but ↑ scattering, ↓ penetration, and competing chromophores (Hgb) occur with lower  $\lambda$  lasers, which is why higher  $\lambda$  used (694+) for hair removal and often for pigmented lesions

**Table 6-24 Lasers**

Laser	Wavelength	Chromophore	Comments
<b>Excimer</b> (XeCl)	308 nm	Protein	Psoriasis
<b>Argon</b>	488 nm, 514 nm	Melanin, Hgb	Vascular and pigmented lesions, ↑ risk scarring
<b>Pulsed dye</b> (short wavelength)	510 nm	Melanin	Pigmented lesions
<b>Copper vapor</b>	511 nm, 578 nm	Melanin, Hgb	Vascular and pigmented lesions
<b>KTP</b> (potassium titanyl phosphate)	532 nm	Melanin, Hgb	Pigmented and superficial vascular lesions
<b>QS Nd:Yag</b> (frequency doubled)	532 nm	Tattoo pigment	Superficial pigmented lesions, red/orange/yellow tattoos
<b>Pulsed dye</b> (PDL)	585–595 nm	Hgb	Vascular lesions, hypertrophic scars, verrucae
<b>Ruby</b>	694 nm	Melanin	Hair removal, nevus of Ota
<b>QS Ruby</b>	694 nm	Melanin, tattoo pigment	Superficial pigmented lesions (i.e., solar lentigo), blue/black/green tattoos
<b>Alexandrite</b>	755 nm	Melanin	Hair removal
<b>QS Alexandrite</b>	755 nm	Melanin, tattoo pigment	Pigmented lesions, blue/black/green tattoos
<b>Diode</b>	800–810 nm	Melanin, Hgb	Hair removal, leg veins
<b>Nd:Yag</b> (long-pulsed)	1064 nm	Melanin, Hgb	Hair removal, nonablative dermal remodeling, leg veins
Concern for retinal damage with Nd:Yag as laser penetrates deep and emits invisible radiation			
<b>QS Nd:Yag</b>	1064 nm	Melanin, tattoo pigment	Pigmented lesions, blue/black tattoos
<b>Nd:Yag</b> (long-pulsed)	1320 nm	Water	Nonablative remodeling
<b>Diode</b>	1450 nm	Water	Nonablative remodeling
<b>Er:Yag</b>	2940 nm	Water	Ablative remodeling
<b>CO<sub>2</sub></b>	10,600 nm	Water	Ablative resurfacing, actinic cheilitis



**Table 6-25 Lasers for Hair Removal**

Laser	Wavelength	Hair Color	Skin Type	Comments
<b>Ruby</b>	694 nm	Blond, red white, gray, brown	I, II	Significant dose-related side effects (epidermal crusting, vesiculation, dyschromia) due to ↑ melanin absorption (vs. Nd:Yag)
<b>Alexandrite</b>	755 nm	Red, gray, brown	I, II	Longer $\lambda$ so ↑ penetration; slightly ↓ risk of epidermal damage than Ruby
<b>Diode</b>	800–810 nm	Brown, black	I, II, III, IV, V	↑ Penetration, ↓ epidermal injury
<b>Nd:Yag</b>	1064 nm	Brown, black	II, IV, V	Deeply penetrating $\lambda$ , ↓ melanin absorption requires ↑ influence for melanin injury; not as effective as Ruby with lighter hair; safe for darker skin types
<b>IPL</b>	515–1200	Varies based of cutoff filters	Varies based on cutoff filters	Nonlaser, noncoherent, multi-wavelength light; filters placed for more selective treatment (shorter $\lambda$ for lighter skin, longer $\lambda$ for darker skin)

**Table 6-26 Lasers for Tattoo Pigment Removal**

Laser Type	Wavelength	Tattoo-Ink Color Treats
<b>Pulsed dye</b> (short wavelength)	510nm (green light)	Yellow, red, orange, purple
<b>QS Nd:Yag</b> (frequency doubled)	532nm (green light)	Red, orange, yellow
<b>QS Ruby</b>	694nm (red light)	Blue, black, green
<b>QS Alexandrite</b>	755nm (red light)	Green, blue, black
<b>QS Nd:Yag</b>	1064nm	Blue, black

Red pigments reflect red light and maximally absorb green light (therefore, ruby/alex is not effective in removing red tattoos); green pigment reflects green light and maximally absorbs red light (so frequency doubled NdYag is not effective)

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# 7

## Pharmacology and Drug Reactions

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## 7.1 ANTI-INFECTIVE MEDICATIONS

### A. Antibiotics

Side effects (SE) listed are either most common or serious

#### Penicillins (PCNs)

- Binds and inactivates bacterial enzymes (PCN-binding proteins) involved in peptidoglycan synthesis → inhibits bacterial cell wall synthesis
- Contains  $\beta$ -lactam ring; drug excretion via kidneys; specific types of PCNs:
  - PCNs with  $\beta$ -lactamase inhibitor: amoxicillin and clavulanate (Augmentin)
  - Penicillinase-resistant PCNs: dicloxacillin, methicillin, oxacillin
- Spectrum: gram-positive (GP) bacteria and spirochetes
- Treats: erysipeloid, anthrax, strep/staph infections, cat/dog/human bites
- SE: morbilliform eruption, angioedema, anaphylaxis, hemolytic anemia, interstitial nephritis, acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN)
- Contraindication (CI): hypersensitivity to any  $\beta$ -lactam antibiotic; pregnancy category B

#### Cephalosporins

- Contains  $\beta$ -lactam ring with same mechanism as PCNs; 10% cross-reactivity with PCNs
- Spectrum of bacterial coverage based upon generation of cephalosporin:
  - First generation: GP > gram-negative (GN); second generation: GP=GN; third generation: GP < GN; fourth generation: GP, GN (little activity against  $\beta$ -lactamase)
- Adverse effects: AGEP, morbilliform eruption (serum sickness associated with cefaclor)
- CI: same as with PCNs; pregnancy category B

#### Tetracyclines (TCNs)

- Binds bacterial ribosomal unit (30s) → blocks bacterial protein synthesis
- Spectrum: GP/GN bacteria, *Chlamydia*, *Mycoplasma*, rickettsia, spirochetes (syphilis, Lyme disease), certain mycobacteria (leprosy); different types of TCNs:
  - **Doxycycline**: excreted in GI tract, so can use in renal failure patients; photosensitivity
  - **Tetracycline**: most common to cause fixed drug eruption and may cause onycholysis, contraindicated in patients <9 years old due to brown discoloration of gingival third of teeth; photosensitivity
  - **Minocycline**: side effect includes blue-black pigmentation of skin/teeth (green-gray discoloration of mid-portion of teeth), drug-induced LE, autoimmune hepatitis
  - **Demeclocycline**: most phototoxic (then doxycycline)
- ↓ Absorption with Fe/Ca<sup>2+</sup>; pregnancy category D

Minocycline treatment of choice for CARP (confluent and reticulated papillomatosis of Gougerot-Carteaud)

#### Macrolides

- Binds bacterial ribosomal unit (50s) → blocks protein synthesis; alternative for PCN-allergic patients; spectrum: GP/GN bacteria, spirochetes, atypical mycobacteria
- Adverse effects: cholestatic hepatitis (estolate form of erythromycin), nausea, diarrhea
- Inhibits cytochrome p450: ↑ levels of p450 substrates like cyclosporine, anticonvulsants, warfarin, digoxin, benzodiazepines, HMG-CoA reductase inhibitors, theophylline (latter combination can cause cardiac arrhythmias); erythromycin + lovastatin → rhabdomyolysis; clarithromycin + CCBs → bradycardia, hypotension
- Pregnancy category C (clarithromycin), category B (erythromycin, azithromycin)

#### Fluoroquinolones (FQs)

- Inhibits bacterial DNA gyrase; spectrum: GN bacteria, strep/staph, certain mycobacteria
- Adverse effects: tendon rupture, cartilage damage in joints, ↑ LFTs, nephrotoxicity
- Contraindication: pregnancy and children (due to deposition of drug in cartilage)



- ↓ Absorption with antacids, iron, sucralfate; inhibits CYP1A2 so ↑ levels of following drugs taken concomitantly: warfarin, aminophylline, theophylline; may also ↑ levels of procainamide; if taken with cyclosporine may increase renal toxicity
- Pregnancy category C

### Clindamycin

- Binds bacterial ribosomal unit (50s) → blocks protein synthesis
- Spectrum: GP and anaerobic bacteria
- SE: pseudomembranous colitis (oral form); pregnancy category B

### Rifampin (Rifampicin)

Only drug bactericidal to *M. leprae*

- Inhibits RNA synthesis by inhibiting DNA-dependent RNA polymerase
- Spectrum: mycobacteria (tuberculosis and leprosy)
- SE: orange-red discoloration of urine/tears, ↓ OCP efficacy; pregnancy category C

### Aminoglycosides

- Binds bacterial ribosomal unit (30s) → blocks protein synthesis; used mainly in topical form
- Spectrum: aerobic GN bacteria; SE (oral): ototoxicity, nephrotoxicity; pregnancy category D

### Sulfonamides

- Sulfamethoxazole and sulfasalazine; interferes with bacterial folic acid synthesis (needed for nucleic acid synthesis) by inhibiting dihydropteroate synthetase
- Spectrum: GP/GN bacteria, *Chlamydia*, *Nocardia*
- SE: hemolytic anemia (especially if G6PD-deficient), nephrotoxicity, hepatotoxicity, TEN, Stevens–Johnson syndrome (SJS), AGEP, photosensitivity
- Contraindication: hypersensitivity to medication, pregnancy (third trimester)
- Pregnancy category C (D in third trimester)

### Dapsone

- Antibacterial and anti-inflammatory (mainly toward neutrophils by inhibition of myeloperoxidase); sulfone family (related to sulfonamides); spectrum: mycobacteria
- Treats: leprosy, dermatitis herpetiformis, autoimmune blistering diseases, erythema elevatum diutinum, pyoderma gangrenosum
- SE: hemolytic anemia (especially if G6PD-deficient), cholestatic jaundice, methemoglobinemia, agranulocytosis (2–12 weeks after continuous treatment), motor peripheral neuropathy, acute psychosis, dapsone hypersensitivity syndrome, photosensitivity
- Pregnancy category C

### Vancomycin

- Inhibits bacterial cell wall synthesis; only given intravenously; spectrum: GP bacteria
- SE: red man syndrome, anaphylaxis, TEN, ototoxicity, phlebitis at IV site
- Pregnancy category B

### Metronidazole (Flagyl)

- Forms toxic metabolites in bacteria, which inhibits nucleic acid synthesis
- Spectrum includes anaerobes and protozoa;
- SE: hypersensitivity, glossitis, disulfiram-like reaction (with alcohol);
- Pregnancy category B

### Clofazamine (Lamprene)

- Unclear mechanism; used for leprosy, erythema nodosum leprosum, DLE; pregnancy category C

## B. Antifungals

**Table 7-1 Oral Antifungal Drugs**

Name	Mechanism of Action	Characteristics
<b>TRIAZOLES</b>		
<b>Itraconazole</b> (Sporonox)	Blocks ergosterol synthesis by inhibiting <b>14<math>\alpha</math>-demethylase</b>	Fungistatic, lipophilic, needs <b>acidic</b> milieu for absorption <b>SE:</b> $\uparrow$ LFTs, $\downarrow$ WBC, $\uparrow$ TG, nephrotoxicity, CHF worsening <b>Tx:</b> dimorphic fungi, aspergillosis, candidiasis, superficial dermatophytes, onychomycosis, sporotrichosis
<b>Voriconazole</b>	<b>Inhibits cyt p450</b> ( $\uparrow$ levels of digoxin, cyclosporine, etc.) Category C	<b>SE: visual disturbances</b>
<b>Fluconazole</b>	<b>Inhibits cyt p450</b> ( $\uparrow$ levels of digoxin, cyclosporine, etc.) Category C	Fungistatic, crosses blood–brain barrier <b>Tx:</b> candidiasis, pityriasis versicolor (PV), cryptococcosis, histoplasmosis, superficial dermatophytes, coccidioidomycosis
<b>IMIDAZOLES</b>		
<b>Ketoconazole</b>	Inhibits <b>14<math>\alpha</math>-demethylase</b> Category C	Fungistatic, lipophilic, needs <b>acidic</b> milieu for absorption, $\uparrow$ absorption with food, <b>inhibits cytochrome p450</b> <b>SE: fulminant hepatitis</b> (rare), $\uparrow$ LFTs (15%), gynecomastia <b>Tx:</b> dermatophytes, candidiasis, dimorphic fungi, PV
<b>ALLYLAMINES</b>		
<b>Terbinafine</b> (Lamisil)	Inhibits <b>squalene epoxidase</b> (first step of ergosterol synthesis) <b>Category B</b>	Fungicidal, biotransformed in liver, does <b>NOT</b> inhibit cyt p450 <b>SE:</b> nausea, metallic taste, liver damage, <b>drug-induced LE</b> <b>Tx:</b> onychomycosis, tinea corporis, tinea pedis
<b>POLYENES</b>		
<b>Amphotericin B</b>	Binds ergosterol and forms membrane pores Category B	<b>SE:</b> acute reaction after infusion (fever, chills, nausea, tachypnea), nephrotoxicity, agranulocytosis, seizures, arrhythmias
<b>OTHERS</b>		
<b>Caspofungin</b>	Inhibits synthesis of <b>glucan</b> (fungal cell wall) Category C	IV administration <b>Tx:</b> candidiasis and aspergillosis
<b>Griseofulvin</b>	Disrupts <b>microtubule function</b> (metaphase arrest) Category C	Fungistatic, $\uparrow$ absorption w/ fatty meal, <b>induces cytochrome p450 (may <math>\downarrow</math> warfarin level)</b> , resistance seen in <i>T. rubrum</i> <b>SE:</b> headache, paresthesias, photosensitivity, <b>drug-induced LE</b> , worsens acute intermittent porphyria <b>Tx:</b> dermatophytes (NOT yeast or bacteria)

Topical antifungal families:

**Imidazoles:** miconazole, clotrimazole, ketoconazole    **Allylamines:** terbinafine, naftifine, butenafine    **Polyenes:** nystatin

## C. Antivirals

**Table 7-2 Oral Antiviral Drugs**

Name	Mechanism of Action	Spectrum, Pregnancy Category	Miscellaneous
<b>Acyclovir</b>	Phosphorylated by <b>viral thymidine kinase</b> to acyclovir monophosphate, which blocks <b>viral DNA polymerase</b> → stops viral DNA synthesis	Herpes simplex virus (HSV), varicella-zoster virus (VZV) Pregnancy category B	<u>SE</u> : IV infusion associated with reversible obstructive nephropathy, rarely may see severe CNS changes (i.e., seizures)
<b>Valacyclovir</b>	Prodrug of acyclovir, same mechanism of action (viral thymidine kinase-dependent activity)	HSV, VZV, cytomegalovirus (CMV) Category B	Better bioavailability than acyclovir <u>SE</u> : TTP/HUS* seen in advanced HIV disease and transplant patients taking high doses
<b>Penciclovir</b>	Phosphorylated by viral thymidine kinase (similar mechanism to acyclovir)	HSV, VZV	Low bioavailability so typically used in topical form
<b>Famciclovir</b>	Prodrug of penciclovir with same mechanism as above	HSV, VZV Category B	Better bioavailability than penciclovir
<b>Ganciclovir</b>	Phosphorylated by viral thymidine kinase; same mechanism as above	CMV (retinitis) Category C	Better activity against CMV than acyclovir; ↓ oral bioavailability <u>SE</u> : neutropenia, bone marrow suppression, mucositis, thrombocytopenia, seizures, hepatic dysfunction
<b>Foscarnet</b>	Noncompetitive inhibition of viral DNA polymerases; analogue of pyrophosphate <b>Does not require phosphorylation</b> so active against acyclovir-resistant viruses	CMV (retinitis), resistant HSV, resistant VZV Category C	Only IV form; active against infections resistant to acyclovir, famciclovir, ganciclovir <u>SE</u> : <b>penile ulcerations or erosions</b> , nephrotoxicity
<b>Cidofovir</b>	Nucleoside analogue, inhibits viral DNA polymerase, <b>independent of thymidine kinase activation</b>	CMV Category C	IV only; active against infections resistant to ganciclovir/foscarnet <u>SE</u> : renal proteinuria, renal toxicity, ↑ creatinine
<b>Amantidine, Rimantidine</b>	Inhibit uncoating of viral DNA within infected host cells (prevents replication)	Influenza A/C, rubella Category C	<u>SE</u> : <b>anticholinergic</b> symptoms, ataxia, and photosensitivity

\*TTP: thrombotic thrombocytopenic purpura

HUS: hemolytic uremic syndrome

**Table 7-3 Antiretroviral Drugs**

Name	Mechanism of Action	Characteristics
<b>Nucleoside/nucleotide reverse transcriptase inhibitors</b>		
<b>Zidovudine (AZT)</b>	Thymidine analogue, inhibits HIV reverse transcriptase (RT)	SE: <b>melanonychia</b> , mucocutaneous pigmentation, bone marrow suppression, lipodystrophy Pregnancy category C
<b>Didanosine (ddI)</b>	Pyrimidine analogue, similar to AZT	SE: pancreatitis, optic neuritis, peripheral neuropathy, lactic acidosis; pregnancy category B
<b>Abacavir (ABC)</b>	Nucleoside RT inhibitor	SE: <b>hypersensitivity reaction</b> (can be fatal upon rechallenge) Pregnancy category C
<b>Tenofovir</b>	Nucleotide analogue, inhibits RT	Peripheral wasting, cushingoid appearance Pregnancy category B
<b>Protease inhibitors</b>		
<b>Indinavir, Ritonavir, Lopinavir</b>	Block HIV-1 protease enzymes	SE: lipodystrophy (buffalo hump), gynecomastia, <b>periungual pyogenic granulomas</b> , paronychia, hepatotoxicity

**D. Anti-parasitic Drugs****Table 7-4 Anti-Parasite Drugs**

Name	Mechanism of Action	Comment
<b>Pyrethrin</b>	Natural extract of chrysanthemum; neurotoxic to lice (not ovicidal)	Contraindicated (CI) if allergy to <b>chrysanthemums</b>
<b>Permethrin</b>	Synthetic pyrethrin; disables nerve cell <b>Na<sup>+</sup> transport channels</b> in parasites → resulting in paralysis	Pediculicidal and ovicidal 2 strengths: 1% (OTC), 5% (Rx) CI: allergy to chrysanthemums
<b>Lindane</b>	Chlorinated hydrocarbon; blocks neural transmission by interfering with <b>GABA</b> → respiratory/muscular paralysis in parasites	Used for scabies, pubic lice, head lice, and body lice SE: ICD, CNS symptoms (i.e., <b>seizures</b> )
<b>Malathion</b>	Organophosphate cholinesterase inhibitor	<b>Flammable</b> ; used in scabies, head lice
<b>Ivermectin</b>	Blocks <b>glutamate-gated chloride channels</b> → paralysis of parasite	Used for strongyloidiasis, onchocerciasis, Norwegian scabies
<b>Crotamiton</b>	Scabicide; unknown mechanism	SE: contact dermatitis
<b>Precipitated sulfur (6%)</b>	Unclear mechanism of action	Treatment for scabies in <b>pregnant women</b> and infants <2 years of age
<b>Thiabendazole, Albendazole</b>	Inhibits <b>fumarate reductase</b> (helminth-specific enzyme)	Used in cutaneous larva migrans SE: dizziness, drowsiness, jaundice
<b>Na<sup>+</sup> stibogluconate, meglumine antimoniate</b>	Pentavalent antimonial; unclear mechanism	Treatment for leishmaniasis SE: pancreatitis, hepatitis, renal failure, <b>prolong QT interval</b>
<b>Pentamidine</b>	Inhibits protozoal DNA/RNA/phospholipid/protein synthesis	Used for trypanosomiasis and leishmaniasis
<b>Diethylcarbamazine (DEC)</b>	Piperazine derivative, unknown mechanism	Used for filariasis, onchocerciasis <b>Mazzotti reaction</b> patient with onchocerciasis treated with DEC → fever, hypotension, tachycardia



## 7.2 IMMUNOSUPPRESSANT DRUGS

### A. Topical Immunosuppressants

#### Topical Glucocorticoids

- Topical form: inhibits epidermal mitosis and DNA synthesis, ↓ collagen cross-linking
- Vasoconstriction directly proportional to anti-inflammatory potency of agent
- SE: atrophy, striae, acneiform eruption, hypertrichosis, hypopigmentation
- Tachyphylaxis: efficacy of topical lost over time; structurally different steroid required
- Pregnancy category C

#### Topical Calcineurin Inhibitors

- Pimecrolimus (Elidel®) and tacrolimus (Protopic®)
- Binds FK506-binding protein, which then inhibits calcineurin (phosphatase) and subsequently blocks T-cell activation; calcineurin typically activated by calcium and calmodulin (bound together), which subsequently causes dephosphorylation of nuclear factor of activated T cells (NFAT) and T-cell activation

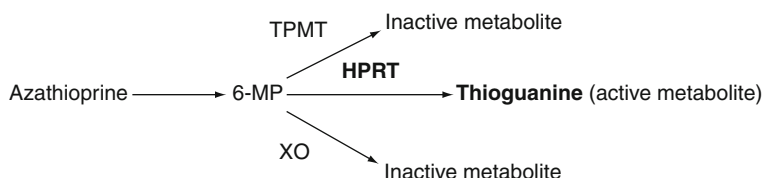
### B. Oral Immunosuppressants

#### Oral Glucocorticoids

- Anti-inflammatory, antimitotic, immunosuppressive, and vasoconstrictive properties; forms complex with intracellular receptors and modulates transcription of certain genes
- Effects
  - ↓ Circulating lymphocytes/eosinophils/monocytes, ↓ macrophage response to lymphokines, ↓ Ab production, ↓ synthesis of proinflammatory molecules, ↓ fibroblast production of collagen
  - ↑ Neutrophils, ↑ blood glucose (stimulates gluconeogenesis), ↑ protein catabolism, ↑ plasma fatty acids/ketone body formation, ↑ acid/pepsin secretion in stomach
- Side effects
  - Cutaneous: atrophy, telangiectasias, striae, poor wound healing
  - Other: ↑ appetite, peptic ulcers, pancreatitis, osteoporosis, Cushing's syndrome, hyperglycemia, hypertriglyceridemia, sodium retention, cataracts, glaucoma, ↑ risk of infection, hypertension, hirsutism, HPA axis suppression, failure to thrive, aseptic necrosis of femoral head, muscle weakness, psychosis, pseudotumor cerebri
- Short-acting glucocorticoids → cortisone and hydrocortisone
  - Greatest mineralocorticoid activity; lowest glucocorticoid activity
- Intermediate and long-acting glucocorticoids → methylprednisolone, triamcinolone, dexamethasone, betamethasone
  - Virtually no mineralocorticoid activity; dexamethasone/betamethasone with highest glucocorticoid activity
- Dosing
  - Single morning dose ↓ risk of HPA suppression
  - Divided daily dosing may ↑ anti-inflammatory efficacy but also ↑ systemic toxicity
  - Alternate day dosing reduces all complications except osteoporosis and cataracts

#### Azathioprine (Imuran) (Figure 7.1)

- Purine analogue which blocks purine synthesis (S-phase-specific); active metabolite is 6-mercaptopurine (6-MP) which is converted to either inactive or active metabolite (6-thioguanine) via one of three enzymatic pathways (TPMT, HPRT, XO):



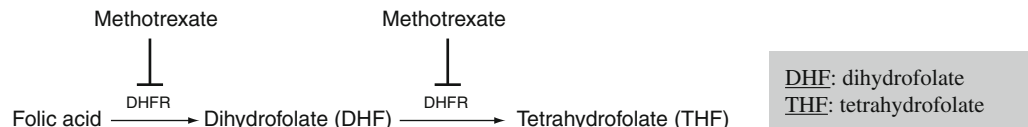
**Figure 7.1**  
Metabolic pathway for azathioprine

TPMT: thiopurine methyltransferase  
HPRT: hypoxanthine phosphoribosyltransferase  
XO: xanthine oxidase

- If XO or TPMT activity inhibited, HPRT becomes primary pathway causing excess toxic purine analogues, which can cause bone marrow suppression; can occur if azathioprine used with allopurinol (which blocks XO) or in patients with genetically low TPMT levels
- Excreted by kidneys
- Check TPMT levels before starting medication
- SE: bone marrow suppression, hypersensitivity syndrome, teratogenicity, lymphoproliferative malignancies (latter only documented in rheumatoid arthritis)
- Pregnancy category D

### Methotrexate (Figure 7.2)

- Antimetabolite and antifolate drug; inhibits dihydrofolate reductase (DHFR) involved in folic acid pathway, which is necessary for DNA/RNA synthesis (via purine and thymidylate synthesis); S phase specific



**Figure 7.2**  
Metabolic pathway inhibited by methotrexate

- Renal excretion; liver biopsy at cumulative dose of 1.5 g; treat acute toxicity with leucovorin; caution in patients with ↑ alcohol intake, diabetes, or renal failure
- SE: hepatotoxicity, pancytopenia, teratogenicity, radiation recall, acral erythema, teratogenicity (egg and sperm), ± lymphoma
- ↑ Pancytopenia risk with concomitant use of: NSAID, dapsone, TMP/SMX, or no folate supplementation; ↑ MTX levels with concomitant use of TCN, phenytoin, phenothiazine, barbiturate, NSAID, salicylate, sulfonamide
- Pregnancy category C

### Mycophenolate Mofetil (Cellcept)

- Inhibits de novo purine synthesis by inhibiting inosine monophosphate dehydrogenase (IMPDH); T and B cells particularly affected; excreted by kidneys
- After ingestion, active metabolite is mycophenolic acid; deactivated by liver but “reactivated” by both epidermis and GI tract
- SE: nausea, vomiting, reversible dose-related bone marrow toxicity, progressive multifocal leukoencephalopathy, pure red cell aplasia
- Caution in peptic ulcer disease; of note, not hepatotoxic or nephrotoxic
- Pregnancy category D

### Cyclophosphamide (Cytosan)

- Nitrogen mustard derivative; cell cycle DNA cross-linkages at any point in cycle
- SE: teratogenicity, ↑ lymphoma risk, ↑ leukemia risk, ↑ bladder cancer risk, ↑ SCC risk, bone marrow suppression, hemorrhagic cystitis (mesna decreases toxicity), azoospermia, pulmonary fibrosis, alopecia, hyperpigmentation of skin/nails
- Treatment of choice for Wegener’s granulomatosis
- Pregnancy category D

**Cyclosporine (CsA)**

**Calcineurin:** a phosphatase activated in the presence of calmodulin and calcium by cyclophilin

- Inhibits T-cell activity by binding to cyclophilin, which subsequently blocks cyclophilin's ability to activate calcineurin; calcineurin regulates NFAT and IL-12, which results in overall inability to produce/release IL-12
- Treatment for psoriasis, pyoderma gangrenosum, severe atopic dermatitis, autoimmune bullous disorders
- SE: nephrotoxicity, reversible hypertension (HTN), gingival hyperplasia, hyperlipidemia, ↑ K and ↓ Mg, ↑ uric acid, paresthesias, hypertrichosis, lymphoma
- Metabolized by cytochrome p450 3A4: inhibitors of cytochrome cause ↑ CsA levels (i.e., diltiazem, nicardipine, verapamil, ketoconazole, fluconazole, itraconazole, erythromycin); inducers of p450 enzymes result in ↓ CsA levels (rifampin, phenobarbital, phenytoin, carbamazepine)
- Check BP regularly; if renal creatinine above 30% of baseline, dose should be reduced
- ↑ Risk for renal toxicity: aminoglycosides, NSAIDs, amphotericin B and vancomycin
- Pregnancy category C

**Hydroxyurea**

- Inhibits ribonucleotide reductase (inhibits DNA synthesis); S phase specific
- SE: hematologic toxicity, photosensitivity, mucosal ulceration, anemia, hepatitis, renal toxicity, poikiloderma of hands/feet, diffuse hyperpigmentation, leg ulcers, radiation recall
- Category D

**Thalidomide**

- Inhibits TNF $\alpha$  but exact mechanism unknown
- Treats: erythema nodosum leprosum, HIV associated mucosal ulceration, recalcitrant DLE or SCLE
- SE: fetal anomalies (phocomelia), peripheral neuropathy (proximal muscle weakness, painful paresthesias of extremities), somnolence, TEN, hypersensitivity reaction, leukopenia

**C. Immunomodulators**

Drug	Mechanism of Action	Side Effects
<b>Interferon</b>	Antiviral and antiproliferative properties	SE: flu-like symptoms, leukopenia, hepatotoxicity
<b>Imiquimod, Resiquimod</b>	Binds TLR7 and induces TNF $\alpha$ , IL-6, and IFN $\alpha$ ; antiviral and antitumor properties	Topical formulation; stimulates both innate and adaptive immune system

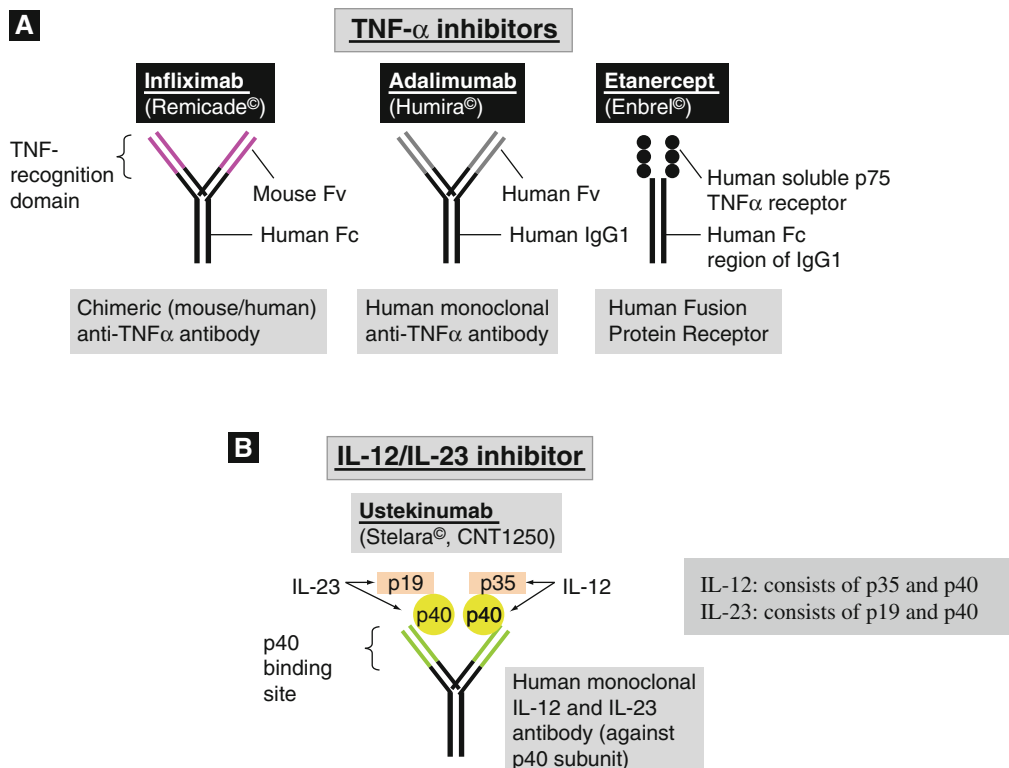
**Table 7-5 Biologically Engineered Immunomodulators**

Name	Route/Category	Mechanism of Action	Others
<b>Etanercept</b> (Enbrel)	Subcutaneous Category B	<b>TNF<math>\alpha</math> inhibitor:</b> fusion protein consisting of TNF $\alpha$ receptor linked to Fc portion of human IgG1; binds free (soluble) TNF $\alpha$	Avoid live vaccines SE: <b>multiple sclerosis</b> , + ANA and LE symptoms, worsening of <b>CHF</b> , serious infections, TB reactivation, malignancy
<b>Infliximab</b> (Remicade)	<b>Intravenous</b> Category B	<b>TNF<math>\alpha</math> inhibitor:</b> chimeric monoclonal Ab against TNF $\alpha$ ( <b>mouse</b> Fv/human IgG1); binds <b>soluble</b> and <b>membrane-bound</b> TNF $\alpha$	Avoid live vaccines SE: infusion reaction, other side effects similar to etanercept
<b>Adalimumab</b> (Humira)	Subcutaneous Category B	<b>TNF<math>\alpha</math> inhibitor:</b> fully <b>human</b> monoclonal Ab against TNF $\alpha$ ; binds <b>soluble</b> and <b>membrane-bound</b> TNF $\alpha$	Same as other TNF $\alpha$ inhibitors
<b>Golimumab</b> (Simponi) (CNTO 148)	Subcutaneous Category B	<b>TNF<math>\alpha</math> inhibitor:</b> fully human monoclonal Ab against TNF $\alpha$	Same as other TNF $\alpha$ inhibitors

*Continued on the next page*

**Table 7-5 Biologically Engineered Immunomodulators (cont'd)**

Name	Route/Category	Mechanism of Action	Others
<b>Certolizumab pegol</b> (Cimzia)	Subcutaneous Category B	<b>TNF<math>\alpha</math> inhibitor:</b> human monoclonal Ab against TNF $\alpha$ ; PEGylated Fab' fragment of human TNF $\alpha$ monoclonal Ab	Same as other TNF $\alpha$ inhibitors
<b>Efalizumab</b> (Raptiva)	Subcutaneous Category C	Humanized form of murine Ab against CD11a, which blocks LFA1 interaction with CAM1; blocks lymphocyte extravasation	<b>Removed from market in 2009</b> due to risk of progressive multifocal leukoencephalopathy (PML)
<b>Alefacept</b> (Amevive)	<b>Intramuscular</b> Category B	Fully human dimeric fusion protein: extracellular domain of LFA3 fused with human Fc portion of IgG1; inhibits CD2/LFA3 interaction thus <b>blocking T-cell activation</b>	Monitor <b>CD4 T-cell count</b> weekly or every other week
<b>Ustekinumab</b> (Stelara) (CNTO 1275)	Subcutaneous Category B	<b>IL-12/IL-23 inhibitor:</b> human IgG1 monoclonal antibody against <b>p40 subunit</b> of IL-12 and IL-23 cytokines (both cytokines share same p40 subunit)	SE comparable to TNF $\alpha$ inhibitors
<b>Briakinumab</b> (ABT-874)	Subcutaneous	IL-12/IL-23 inhibitor	Currently under investigation
<b>AIN-547</b>		Monoclonal antibody against IL-17	Currently under investigation

**Figure 7.3****A: TNF $\alpha$  inhibitors    B: IL-12/IL-23 inhibitor**



## D. Antimalarials

### Hydroxychloroquine (Plaquenil)

- Most likely intercalates into DNA, preventing further translation/transcription; immunosuppressive and anti-inflammatory effect
- Treatment for DLE, SLE, dermatomyositis, photosensitivity dermatoses (i.e., polymorphous light eruption), sarcoidosis, granuloma annulare, porphyria cutanea tarda (PCT)
- SE: accumulates in melanin-rich tissue (i.e., choroid); ocular toxicity can manifest as retinopathy (potentially irreversible), mucocutaneous and nail blue-gray pigmentation (hemosiderin and melanin deposition), hemolysis (mainly in G6PD deficiency), bleaching of hair roots, alopecia
- Premaculopathy (changes in visual field) is reversible; true retinopathy with bull's eye pigment deposition is not reversible
- Do not give both chloroquine and hydroxychloroquine because additive retinotoxic effect (add quinacrine instead)
- Pregnancy category C

### Chloroquine (Aralen)

- Anti-inflammatory and immunosuppressive agent; accumulates in lysosomes, inhibits chemotaxis and phagocytosis
- SE: ocular toxicity, yellow discoloration of skin and sclera, bleaching of hair root, pancytopenia, EKG changes
- Risk of retinopathy greatest with chloroquine

### Quinacrine

- Side effects similar to other antimalarials, but no risk of retinopathy

## E. Chemotherapy Agents

Table 7-6 Chemotherapy Agents

Name	Mechanism of Action	Side Effects
<b>Chlorambucil</b>	Alkylating agent derived from nitrogen mustard	SE: bone marrow suppression, urticaria, mucositis
<b>5-Fluorouracil (5-FU)</b>	Cell cycle-specific pyrimidine antagonist, blocks DNA/RNA synthesis	SE: extravasation reaction (infusion), chemotherapy recall, <b>inflammation of AKs</b>
<b>Bleomycin</b>	<b>M- and G2-phase-specific</b> → damages DNA by direct binding	SE: <b>Raynaud's phenomenon</b> (with periungual wart treatment), pulmonary toxicity, <b>flagellate hyperpigmentation</b>
<b>Doxorubicin (Adriamycin)</b>	Cytotoxic antibiotic: intercalates with preformed DNA residues blocking DNA/RNA transcription	SE: <b>cardiac toxicity</b> , mucositis, chemotherapy recall, radiation recall
<b>Dactinomycin (Actinomycin)</b>	Cytotoxic antibiotic: complexes w/ DNA, blocks DNA/RNA/protein synthesis	SE: <b>radiation recall</b>
<b>Vinblastine</b>	Periwinkle plant extract, cell-cycle-specific (arrests in <b>metaphase</b> )	Vincristine analogue of vinblastine SE: extravasation reaction (vincristine)
<b>Cytarabine</b>	Blocks DNA synthesis in <b>S phase</b>	SE: acral erythema, <b>neutrophilic eccrine hidradenitis</b> , eccrine squamous syringometaplasia, <b>inflammation of SKs</b>

## 7.3 OTHER DRUGS

### Retinoids

- Class of natural and synthetic compounds chemically related to vitamin A
- Vitamin A exists in three interconvertible forms: retinol (vitamin A alcohol), retinal (aldehyde), retinoic acid (acid)
- Function
  - Normalizes keratinization (allowing for decrease in follicular occlusion): inhibits ornithine decarboxylase, inhibits collagenase, downregulates proliferative keratins (K6 and K16), increases filaggrin production/keratin filaments/KHGs, antagonizes function of AP-1 and IL-6, downregulates TLR2
- Binds two types of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs)
  - **RARs**: all-trans RA ligand, RAR $\gamma$  is the most ubiquitous RAR in human skin and likely main mediator of retinoid effects on keratinocytes, nuclear receptors activated and gene transcription affected
  - **RXRs**: cis RA ligand, receptors activated in bexarotene
- Retinoids classified into three generations (see Table 7-7)
- **Isotretinoin**
  - 13-cis retinoic acid; increased absorption with fatty meal; half-life 18–20 h; goal cumulative dose 120–150 mg/kg (0.5–2 mg/kg/day for 16–20 weeks); start with lower dose in markedly inflammatory acne
  - Results in atrophy of sebaceous glands, reduction in sebum (up to 90%) so *P. acnes* unable to thrive, normalization of follicular keratinization
  - Treatment for nodulocystic acne, recalcitrant inflammatory acne, pyoderma faciale, acne fulminans, and gram-negative folliculitis
  - Females must avoid pregnancy for at least 1 month after discontinuing drug
  - Side effects: cheilitis, xerosis, alopecia, skin fragility, eczematous dermatitis, photophobia, keratitis, myalgias (associated with  $\uparrow$  creatine phosphokinase levels), headache, pseudotumor cerebri (with concomitant TCN use), skeletal hyperostosis, premature closure of epiphyseal plates, teratogenicity, elevated triglycerides (25–45%, most common lab abnormality), elevated liver transaminases, reduced night vision, pyogenic granulomas, staph colonization
  - Retinoid teratogenicity: craniofacial, cardiac, thymic, and CNS malformations
- **Acitretin**:
  - Metabolite of etretinate; half-life 2 days
  - Females must avoid pregnancy for at least 3 years after discontinuing acitretin (since drug can re-esterify to etretinate, which is highly lipophilic with 120 day half-life)
  - Side effects: teratogenicity, hyperlipidemia, alopecia, arthralgias, abnormal liver function tests, reduced night vision, bone and joint pain, pseudotumor cerebri, xerosis of mucous membranes
- **Bexarotene**:
  - RXR-specific retinoid; approved for treatment of cutaneous T-cell lymphoma (CTCL); half-life 7–9 h; metabolized by cytochrome p450 enzymes and elimination via hepatobiliary system
  - SE: similar to other retinoids with addition of drug-induced hypothyroidism

Gemfibrozil may increase plasma level of bexarotene

Table 7-7 Retinoids

Generation of Retinoid	Name	Half-life
First generation	Tretinoin (all-trans RA)	Half-life: 48 min
	Isotretinoin (13-cis RA)	Half-life: 20 h
Second generation	Etretinate	Half-life: 120 days (highly lipophilic)
	Acitretin	Half-life: 50 h
Third generation	Tazarotene, Adapalene Bexarotene	Half-life: 7 h

## Hormone-Related Drugs

**Table 7-8 Hormone-Related Drugs**

Name	Mechanism of Action	Others
<b>Spironolactone</b> (Aldactone)	Antiandrogen: blocks dihydrotestosterone (DHT) from binding to receptor Category C	Treats: hirsutism, hormonal acne (especially in PCOS), androgenetic alopecia SE: ↑ <b>K<sup>+</sup> level</b> , gynecomastia, breast tenderness (most common), and menstrual irregularity
<b>Finasteride</b> (Propecia) (Proscar)	Inhibits type II 5 $\alpha$ -reductase (which converts testosterone to DHT) Category X	Treats: androgenetic alopecia SE: ↓ libido, erectile dysfunction, teratogen
<b>Flutamide</b>	Nonsteroidal antiandrogen: blocks DHT binding to R Category D	Treats: hirsutism (usually combined with OCP) SE: hepatotoxicity
<b>Stanozolol</b> <b>Danazol</b>	Synthetic anabolic steroid derived from testosterone Category X	Treats: C1 esterase inhibitor deficiency, microvascular occlusion syndrome, and cryofibrinogenemia (due to fibrinolytic activity) SE: alopecia, hirsutism, acne, hypertension, insulin resistance, muscle cramps
<b>Oral contraceptive pill</b> (OCP)	Typically combination of estrogen and progestin (typically with low-androgenic activity)	Blocks both ovarian and adrenal androgen production; used in hormonal acne  <u>Low-androgenic progestins</u> : norethindrone, levonorgestrel, desogestrel, norgestimate
<b>Eflornithine hydrochloride</b> (Vaniqa)	Irreversibly inhibits ornithine decarboxylase (ODC) Category C	Slows down hair growth since ODC important for hair proliferation and growth; topical cream Treats: hirsutism
<b>Minoxidil</b> (Rogaine)	Mechanism not fully understood Category C	Two topical formulations: 2% and 5% Treats: alopecia SE: contact dermatitis, rarely HA or chest pain

## Antihistamines

- Competitive inhibitor (reversible) of histamine at tissue receptor sites; H1 and H2 blockers
- H1 antihistamines divided into first and second generation
- First generation:** diphenhydramine, promethazine, cyproheptadine, chlorpheniramine, hydroxyzine
  - SE: drowsiness and anticholinergic symptoms (blurry vision, urinary retention, dry mouth, constipation)
  - Cyproheptadine:** treatment of choice for cold urticaria
  - Chlorpheniramine:** safest in pregnancy
  - Hydroxyzine:** side effects include EKG changes, arrhythmias
- Second generation:** fexofenadine, loratidine, cetirizine, levocetirizine
  - SE: drowsiness and anticholinergic symptoms
  - Fexofenadine:** few sedative effects, few to no anticholinergic symptoms, category C
  - Loratidine:** long-acting, minimally sedating, category B
  - Cetirizine:** low sedation, metabolite of hydroxyzine,  $\pm$  anticholinergic effect, category B
- H2 antihistamines (cimetidine, ranitidine)

- Cimetidine: competitively inhibits DHT at androgen receptor site (side effects include gynecomastia, impotence, loss of libido)
- Others
  - **Doxepin**: tricyclic antidepressant, H1/H2 antihistamine, inhibits histamine and acetylcholine, anticholinergic, cardiotoxic (may prolong QT interval); side effects: conduction disturbances, seizure disorder, urinary retention
  - **Amitriptyline**: tricyclic antidepressant with some H1 blocking activity, side effects include anticholinergic symptoms and risk of cardiac arrhythmias
  - **Cromolyn sodium**: blocks mast cell degranulation
  - **Montelukast, zafirlukast**: leukotriene receptor antagonist
  - **Zileuton**: inhibitor of 5-lipoxygenase, which subsequently inhibits leukotriene formation

## Phototherapy

- Includes UVB (narrowband or broadband) and UVA (UVA1 or UVA2 ± psoralen)
- CI: photosensitizing medication (i.e., thiazides) and photosensitive disorders (i.e., lupus)
- **Broadband UVB** (290–320 nm): emits light in broad range, not used as frequently now
- **Excimer Laser** (308 nm): targeted phototherapy for recalcitrant psoriatic lesions
- **Narrowband UVB (NBUVB)** (311–313 nm): narrower spectrum relates to better therapeutic effect than broadband
  - Possible mechanism of action: UV light absorption by chromophores (i.e., nuclear DNA) resulting in DNA photoproducts like pyrimidine dimers, ↓ cellular proliferation, apoptosis of T cells, suppression of Langerhans cells
  - Erythema after 4–6 h, peaks at 12–24 h; can use in pregnant women and children
  - SE: erythema/blistering (acute), photoaging, carcinogenesis
- **UVA**: UVA2 (320–340 nm, similar to UVB) and UVA1 (340–400 nm, penetrates deep)
- **PUVA** (typically peaks at 352 nm): UVA + psoralen (type of furocoumarin, topical or oral)
  - Oral psoralen (i.e., methoxsalen): peak concentration occurs 1.5 h after ingestion
  - Ocular toxicity: may detect psoralen in lens for up to 12 h after ingestion, thus patients to avoid sun exposure for 24 h after PUVA treatment
  - Mechanism of action: intercalates into DNA, forms reactive oxygen species (ROS), alters cytokine expression, ↓ cellular proliferation, results in apoptosis of T cells, and suppresses Langerhans cells
  - Erythema after 24–36 h later and peaks at 48–96 h
  - SE: diffuse hyperpigmentation, nausea, vomiting, stinging, pruritus (may be intense), PUVA lentigines, photoaging, carcinogenesis
- **Extracorporeal photochemotherapy (ECP)**: extracorporeal UVA irradiation of WBCs after 8-MOP added, then returned back to patient; used in treatment of erythrodermic CTCL
- **Photodynamic therapy (PDT)**: 400–700 nm
  - Topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) transformed into protoporphyrin IX (higher amounts found in tumors); with exposure to red or blue light, ROS produced and selectively destroys premalignant and malignant cells
  - Therapeutic wavelength between 400 and 800 nm but typically blue light (near 400 nm) chosen due to large porphyrin absorption peak



Table 7-9 Miscellaneous Drugs

Name	Mechanism of Action	Others
<b>Cochicine</b>	Alkaloid preventing microtubule assembly (metaphase arrest), decreases neutrophil chemotaxis, degranulation, and adhesion	Tx: neutrophilic dermatoses (Sweet's, Behcet's, etc.), aphthous stomatitis SE: GI ( <b>diarrhea</b> ), peripheral neuropathy, myopathy
<b>Potassium iodide</b> (SSKI)	Likely suppresses neutrophil migration and toxicity  Wolff-Chaikoff effect: inhibits thyroid hormone synthesis due to ↑↑ iodide (blocks organic iodine)	Treats: several types of panniculitis, neutrophilic disorders, sporotrichosis (cutaneous) SE: acneiform eruption, hypothyroidism (check TSH 1 month after starting), iododerma
<b>Gold</b>	Inhibits neutrophil/macrophage chemotaxis and phagocytosis, blocks prostaglandin synthesis	Tx: severe DLE/SLE, bullous diseases SE: lichenoid eruption, cheilitis, diarrhea
<b>Calcipotriene</b> (Calcipotriol)	Synthetic vitamin D <sub>3</sub> derivative, similar effect as calcitriol	Cream, ointment, or lotion SE: irritation, burning
<b>Calcitriol</b> (1,25[OH] <sub>2</sub> D <sub>3</sub> )	Active form of vitamin D <sub>3</sub> , inhibits keratinocyte proliferation	SE: possible hypercalcemia, hypercalciuria
<b>Anthralin</b> (Dithranol)	Antiproliferative property; likely inhibits cell growth	Topical used in psoriasis and alopecia areata SE: odor, staining property, irritation
<b>Coal tar</b>	Crude distillate; anti-inflammatory, antiproliferative properties	Used for inflammatory dermatoses (psoriasis) SE: odor, staining property, contact dermatitis
<b>Hydroquinone</b>	Reversible depigmentation: inhibition of enzyme tyrosinase (blocks tyrosine to melanin)	Used for melasma SE: irritation, ochronosis (rare)
<b>Alendronate, Risedronate, Pamidronate</b>	Bisphosphonate, inhibits osteoclasts with ↓ bone turnover, ↑ mineralization density of bone	Used in long-term oral corticosteroid therapy SE: severe musculoskeletal pain, osteonecrosis CI: <b>pregnancy</b> , hypocalcemia, renal failure
<b>Pentoxifylline</b>	Fibrinolytic and anti-thrombotic properties, improves blood flow	Used for venous ulcers SE: GI upset, dizziness
<b>Glycopyrrolate</b>	Oral anticholinergic resulting in decreased sweating	Used for hyperhidrosis SE: anticholinergic symptoms
<b>Pimozide</b> (Orap)	Antipsychotic drug: blocks dopaminergic receptors in CNS	Used in delusions of parasitosis SE: <b>prolongs QT interval</b> , extrapyramidal reactions, tardive dyskinesia
<b>Nicotinamide</b> (Niacinamide)	Part of vitamin B group, anti-inflammatory property	Topical formulation mainly used in dermatology
<b>Azelaic acid</b>	Dicarboxylic acid; ↓ oxidative tissue injury with inflammation	Used in postinflammatory hyperpigmentation, melasma, rosacea, acne; category B
<b>Podophyllin</b>	Antimitotic, arrests cells in metaphase by binding tubulin	Used for condyloma acuminata Contraindicated in pregnancy
<b>Benzoyl peroxide</b>	Bacteriostatic against <i>P. acnes</i> , causes oxidation of bacterial protein, keratolytic, desquamative	SE: irritation, dermatitis, swelling, crusting, bleaching of colored fabrics and hair
<b>Sulfur</b>	Antifungal, antibacterial, and keratolytic effect	Often used with sodium sulfacetamide SE: dryness, itching

## Pregnancy Category

- A: considered safe in pregnancy
- B: animal reproduction studies have failed to demonstrate risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
- C: animal reproduction studies have shown adverse effect on fetus but there are no adequate and well-controlled studies in humans
- D: positive evidence of human fetal risk
- X: contraindicated in pregnancy

**Table 7-10 Pregnancy Categories**

Category B	Category C	Category D	Category X
Pencillins	Fluoroquinolones	Aspirin (C or D)	Bexarotene
Erythromycin (not estolate form)	Trimethoprim sulfamethaxazole	Azathioprine	Acitretin
Azelaic acid	Cyclosporine	Bleomycin	Estrogens (conjugated)
Cephalosporins	Acyclovir	Colchicine	Finasteride
Lidocaine	Fluconazole	Cyclophosphamide	5-FU
Etanercept	Ketoconazole	Hydroxyurea	Tazarotene
Alefacept	Itraconazole	Mechlorethamine	Isotretinoin
Infliximab	Benzoyl peroxide	Penicillamine	Methotrexate
Cyproheptadine	Topical tretinoin	Potassium iodide	Stanozolol
Cetirizine	Topical/oral steroids	Tetracycline	Thalidomide
Loratidine	Griseofulvin	Flutamide	
	Fexofenadine		
	Epinephrine		
	Sodium sulfacetamide		
	Spironolactone		

## 7.4 DRUG REACTIONS AND INTERACTIONS

### Cytochrome P450 Enzymes (Table 7-11)

- Major drug-metabolizing enzymes that are most predominant in the liver but can also be found in other organs (i.e., intestine, lung)
- Drug interaction involving p450 enzymes typically occur from one of two processes: enzyme inhibition or enzyme induction
- Enzyme inhibition: competition with another drug for the enzyme-binding site
- Enzyme induction: drug stimulates synthesis of more enzyme protein, enhancing metabolizing capacity of the enzyme
- Different isoforms: CYP2D6, CYP3A4 (most abundant cytochrome enzymes in humans and involved in many clinically important drug interactions), CYP1A2, CYP2C9, CYP2E1, CYP2C19
- Many drugs are substrates (metabolized by specific p450 isoenzyme) but unable to inhibit or induce the p450 enzymes

Table 7-11 Cytochrome p450 Drugs

Cytochrome p450 Substrates		3A4 Inducers	3A4 Inhibitors
<b><u>Anti-arrhythmics</u></b>	<b><u>Calcium Channel Blocker (CCB)</u></b>	<b><u>Anticonvulsants</u></b>	<b><u>Antidepressants</u></b>
Digoxin	Nifedipine	Phenytoin	Fluoxetine
Quinidine	Diltiazem	Phenobarbital	Paroxetine
Amiodarone	Verapamil	Carbamazepine	Sertraline
<b><u>Antibiotics</u></b>	Felodipine	<b><u>Anti-TB drugs</u></b>	<b><u>Azole Antifungals</u></b>
Erythromycin	<b><u>Immunosuppressants</u></b>	Isoniazid	Ketoconazole
Clarithromycin	Tacrolimus	Rifampin	Itraconazole
Rifampin	Cyclosporine	<b><u>HIV antivirals</u></b>	Fluconazole
<b><u>Anticonvulsants</u></b>	Dapsone	Ritonavir	<b><u>Antibiotics</u></b>
Phenytoin	Cyclophosphamide	<b><u>Miscellaneous</u></b>	Erythromycin
Carbamazepine	<b><u>Protease Inhibitors</u></b>	Propranolol	Clarithromycin
Ethosuximide	Indinavir	St. John's Wort	Ciprofloxacin
<b><u>Antidepressants</u></b>	Ritonavir	Omeprazole	Metronidazole
Amitriptyline	Saquinavir	Griseofulvin	<b><u>CCBs</u></b>
Doxepin	<b><u>Statins</u></b>		Verapamil
Sertraline	Atorvastatin		Nifedipine
Imipramine	Lovastatin		Diltiazem
<b><u>Antihistamines</u></b>	Simvastatin		<b><u>Miscellaneous</u></b>
Fexofenadine	<b><u>Miscellaneous</u></b>		Cimetidine
Terfenadine	Glyburide		Cyclosporine
Astemizole	Pimozide		Quinine
	Theophylline		Grapefruit Juice
	Warfarin		Warfarin
			<b><u>Protease Inhibitors</u></b>
			Ritonavir
Warfarin + phenobarbital/rifampin/phenytoin → <b>decreased</b> levels of warfarin			
Warfarin + cimetidine/erythromycin/itraconazole/ketoconazole → <b>increased</b> levels of warfarin			
Cyclosporine + itraconazole → <b>increased</b> levels of cyclosporine			

**Table 7-12 Drug Reactions**

Reaction	Culprit drugs
<b>Acneiform lesions</b>	Corticosteroids, androgenic steroids, phenytoin, INH, lithium, halogens, (bromides, iodides), <b>epidermal growth factor receptor inhibitors</b> (EGFRI) such as <b>erlotinib, cetuximab, gefitinib</b>
<b>Acral erythema</b> (erythrodysesthesia)	<b>Doxorubicin, daunorubicin</b> , 5-fluorouracil, <b>cytarabine</b> , docetaxel, methotrexate (MTX)
<b>Acral sclerosis</b>	Bleomycin
<b>AGEP</b> (acute generalized exanthematous pustulosis)	<b><math>\beta</math>-lactam antibiotics</b> , macrolides, calcium channel blockers (i.e., diltiazem), chloroquine, terbinafine
<b>Alopecia</b>	Alkylating agents (i.e., cyclophosphamide), anthracyclines (doxorubicin, daunorubicin), taxanes (paclitaxel, docetaxel), vincristine, vinblastine, actinomycin-D, etoposide
<b>Autoimmune hepatitis</b>	<b>Minocycline</b> (MCN)
<b>Bullous pemphigoid</b>	<b>Furosemide, PCN, captopril, <math>\beta</math>-blockers</b> , sulfonamides, terbinafine, penicillamine
<b>Dermatomyositis-like eruption</b>	<b>Hydroxyurea</b> , penicillamine, statins
<b>Ecchymotic squamous syringometaplasia</b>	<b>Cytarabine</b> , cyclophosphamide, <b>paclitaxel, docetaxel</b> , busulfan, carmustine
<b>Elastosis perforans serpiginosa (EPS)</b>	<b>D-penicillamine</b>
<b>Erythema nodosum</b>	OCPs, antibiotics ( <b>sulfonamides</b> , tetracyclines), NSAIDs
<b>Extravasation reaction</b> (ulcer, chemical cellulitis)	Anthracyclines ( <b>doxorubicin/daunorubicin</b> ), actinomycin-D, docetaxel, paclitaxel, vinblastine, vincristine, etoposide, 5-fluorouracil (5-FU)
<b>Fixed drug eruption (FDE)</b>	<b>NSAIDs (naproxen)</b> , <b>sulfonamides</b> , <b>TCNs</b> , acetaminophen, aspirin, OCP, <b>phenolphthalein</b> , <b>pseudoephedrine</b> (non-pigmenting variant), barbiturates
<b>Flag sign</b> (of chemo)	<b>MTX</b> (horizontal hyperpigmented bands of hair alternating w/ normal color)
<b>Gingival hyperplasia</b>	<b>Phenytoin, cyclosporine, CCBs</b> (i.e., nifedipine, amlodipine)
<b>Hyperpigmentation</b>	Antimalarials, clofazamine (violet-brown to blue in lesional skin), imipramine, amiodarone (blue-gray), phenothiazines (chlorpromazine, promethazine, prochlorperazine), chemotherapeutics (busulfan, cyclophosphamide, hydroxyurea, dactinomycin, MTX, 5-FU), and minocycline (see below):  <div> <div>MCN pigmentation</div> <div> <div></div> <div></div> <div></div> </div> </div> <div> <b>Type 1:</b> blue-black color within scars, + iron (hemosiderin) with <b>Perls stain</b>  <b>Type 2:</b> blue-gray color on shins, + melanin (<b>Fontana-Masson stain</b>), + iron (<b>Perls stain</b>)  <b>Type 3:</b> generalized “muddy brown” hyperpigmentation in sun-exposed sites (<math>\uparrow</math> melanin within epidermis, no iron deposition) </div>
<b>Hypersensitivity syndrome</b>	Aromatic anticonvulsants ( <b>phenytoin, phenobarbital, carbamazepine</b> , lamotrigine, oxcarbazepine), sulfonamides, allopurinol, dapsone, gold, olanzapine, saquinavir
<b>Hypertrichosis</b>	Cyclosporine, phenytoin, minoxidil, danazol, anabolic steroids
<b>Inflamed AKs</b>	<b>5-fluorouracil</b> , capecitabine, pentostatin
<b>Inflamed SCC</b>	<b>Fludarabine</b>
<b>Inflamed SKs</b>	<b>Cytarabine</b> , docetaxel
<b>Leg ulcers</b>	<b>Hydroxyurea</b>
<b>Leukocytoclastic vasculitis</b>	Antibiotics (especially <b><math>\beta</math>-lactam antibiotics</b> ), NSAIDs, diuretics
<b>Lichenoid eruption</b>	Penicillamine, gold, <b>hydrochlorothiazide (HCTZ)</b> , furosemide, <b><math>\beta</math>-blockers</b> (propranolol, labetalol), ACEI (captopril, enalapril), chlorpromazine, <b>antimalarials</b> (chloroquine, hydroxychloroquine, quinacrine), <b>quinidine</b>



Table 7-12 Drug Reactions (cont'd)

Reaction	Culprit drugs
<b>Linear IgA bullous dermatosis (LABD)</b>	<b>Vancomycin, <math>\beta</math>-lactam antibiotics, NSAIDs, captopril</b> , phenytoin, sulfonamides, <b>furosemide</b> , amiodarone, lithium
<b>Localized hyperpigmentation</b>	<u>Flagellate hyperpigmentation</u> : <b>bleomycin</b> <u>Supravenous serpentine hyperpigmentation</u> : <b>5-FU</b> <u>Sun-exposed hyperpigmentation</u> : daunorubicin, 5-FU, MTX <u>Mucosal</u> : busulfan, cyclophosphamide, 5-FU, hydroxyurea, doxorubicin <u>Occluded areas</u> : <b>thiotepa</b> , ifosfamide, topical carmustine, docetaxel, cisplatin
<b>Lupus</b>	SCLE: <b>HCTZ, griseofulvin, terbinafine</b> , CCBs SLE: hydralazine, procainamide, isoniazid, MCN, phenytoin, penicillamine
<b>Melanonychia</b>	Chemotherapeutics (melphalan, hydroxyurea, bleomycin, capecitabine, doxorubicin), lamivudine, MCN, <b>zidovudine (AZT)</b>
<b>Mucositis</b>	Cyclophosphamide, daunorubicin, doxorubicin, MTX (high dose), 5-FU
<b>Neutrophilic eccrine hidradenitis</b>	Doxorubicin, daunorubicin, <b>cytarabine</b> , 5-FU, MTX, bleomycin, cyclophosphamide, busulfan, taxanes
<b>Onycholysis</b>	Paclitaxel, docetaxel, etoposide, retinoids, doxorubicin, captopril Photo-onycholysis: TCN, OCPs, fluoroquinolones, psoralens
<b>Orange-red body fluid</b>	<b>Rifampin</b>
<b>Pemphigus vulgaris</b>	Thiol drugs ( <b>penicillamine, captopril, lisinopril</b> , piroxicam, gold sodium thiomalate), penicillins, cephalosporines, quinolones, rifampicin, phenylbutazone, propranolol, carbamazepine
<b>Penile ulcers</b>	<b>Foscarnet</b>
<b>Photosensitivity</b> (includes allergic and toxic reactions)	Griseofulvin, NSAIDs, phenothiazines, sulfonamides, thiazides, dapsone, MTX, hydroxyurea, 5-FU, fluoroquinolones, TCNs, furosemide, diltiazem, isotretinoin, imipramine, chlorpromazine, phenothiazines
<b>Pseudoporphyria</b>	NSAIDs (naproxen, piroxicam), nalidixic acid, furosemide, HCTZ, isotretinoin, TCNs, sulfonamides
<b>Pseudotumor cerebri</b>	TCN, isotretinoin
<b>Pseudoxanthoma elasticum (PXE)</b>	Penicillamine
<b>Psoriasis</b> (induce/worsen)	Terbinafine, NSAIDs, antimalarials, ACEI, lithium, $\beta$ -blockers
<b>Pulmonary fibrosis</b>	MTX, bleomycin, busulfan, amiodarone, gold, penicillamine
<b>Radiation recall</b>	Doxorubicin, daunorubicin, paclitaxel, docetaxel, MTX, actinomycin-D, capecitabine, gemcitabine, bleomycin
<b>Raynaud's phenomenon</b>	Combination of bleomycin and vinblastine
<b>Sweet's syndrome</b>	<b>Granulocyte colony-stimulating factor (GCSF)</b> , carbamazepine, trimethoprim-sulfamethoxazole (TMP-SMZ)
<b>Toxic epidermal necrolysis (TEN)</b>	Allopurinol, PCNs, anticonvulsants (carbamazepine, lamotrigine, phenytoin), sulfonamides, antiretrovirals, barbiturates, NSAIDs

### Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

- Also known as “hypersensitivity syndrome”; represents serious hypersensitivity reaction to a drug, typically appearing 2–6 weeks after starting offending medication
- Characterized by cutaneous eruption, fever, lymph node enlargement, and internal organ involvement (elevated eosinophils, elevated liver enzymes with possible fulminant hepatitis, interstitial nephritis, etc.)
- Presents with morbilliform eruption which may become more edematous with follicular accentuation;  $\pm$  vesicles, tense bulla, erythroderma; typically involves upper trunk, extremities and face; hallmark finding is facial edema
- Related drugs: sulfonamides, phenobarbital, carbamazepine, phenytoin, lamotrigine, allopurinol, dapsone, abacavir

- Likely related to the inability to detoxify toxic arene metabolites in anticonvulsant drugs; of note, aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital) are known to cross-react with one another, and safe alternatives include levetiracetam and valproic acid
- Treatment: topical corticosteroid for cutaneous eruption, systemic corticosteroid if internal organ involvement

### Acute Generalized Exanthematous Pustulosis (AGEP)

- Febrile drug reaction often seen within 1–2 days of starting offending drug
- Presents with punctate non-follicular sterile pustules in a background of edematous erythema; lesions appear initially on face or intertriginous areas and spread to trunk and upper extremities;  $\pm$  edema of face and hands; resolves typically within 1–2 weeks with superficial desquamation
- Related drugs:  $\beta$ -lactam antibiotics, macrolides, calcium channel blockers (i.e., diltiazem), antimalarials, terbinafine, carbamazepine, acetaminophen
- Treatment: remove offending drug, topical corticosteroid

### Neutrophilic Eccrine Hidradenitis (NEH)

- Presents with erythematous papules and plaques involving trunk and/or extremities
- Most often reported in patients with acute myelogenous leukemia taking cytarabine, but may be seen with other chemotherapeutics and non-chemotherapeutics (i.e., acetaminophen)
- Histology: neutrophilic infiltrate around eccrine glands
- Treatment: often self-limited

### Anticoagulant-Induced Skin Necrosis

- Rare reaction typically seen 2–5 days after offending drug started; typically due to warfarin or heparin; likely related to drop in protein C level
- Present with painful erythematous plaque that turn into necrotic ulcers and or bullae due to ischemic infarcts; typically seen on buttocks, thighs, or breasts
- Treatment: stop offending drug, vitamin K, IV concentrate of protein C

### Erythema Multiforme

- Acute, often self-limited skin condition associated with infection (mainly herpes) or medication (less common) and rarely systemic disease; two types: EM minor and EM major
- Presents with abrupt onset of “target” lesions on face and distal extremities; target lesions often appear as dusky circinate plaques with concentric rings of color,  $\pm$  bulla, vesicle or crust in center of lesion; may also see atypical papular target lesions; no mucosal or systemic involvement in EM minor
- Treatment: typically self-limited within 2 weeks, prophylactic antiviral if HSV-related EM with frequent recurrences

### Stevens–Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

- Rare, life-threatening mucocutaneous reaction almost always drug-related (rarely due to infection or immunizations) with 25–50% mortality for TEN and much less for SJS
- Presents with poorly demarcated dusky erythematous or purpuric macules, papules, patches, or plaques that subsequently result in flaccid bullae or frank epidermal detachment due to necrosis of the epidermis; often starts on the trunk and spreads to face, proximal upper extremities and neck; erythema with painful mucosal erosions/ulcerations involving genital, buccal, and ocular mucosa seen in most cases;  $\pm$  Nikolsky sign (dermal-epidermal cleavage with tangential pressure on normal appearing skin),  $\pm$  Asboe-Hansen sign (bullae extend laterally with pressure);  $\pm$  palmoplantar involvement;  $\pm$  respiratory and GI epithelial involvement

- TEN > 30% BSA with skin detachment; SJS/TEN overlap with 10–30% involvement; SJS with < 10% BSA involvement
- Offending drugs: antibiotics (**sulfonamides**, **PCNs**), **allopurinol**, anticonvulsants (**carbamazepine**, **lamotrigine**, **phenytoin**), barbiturates, NSAIDs, antiretrovirals
- Poor outcome associated following (SCORTEN): age > 40, heart rate >120 bpm, BSA > 10% on day 1, ↑ serum urea >27 mg/dl, serum bicarbonate >20 mmol/l, ↑ glucose >250 mg/dl, underlying cancer or hematologic malignancy
- Complications: symblepharon, synechiae, cutaneous scarring, eruptive nevi, phimosis, nail dystrophy, alopecia, blindness
- Histology: full-thickness epidermal necrosis; early lesions with apoptotic keratinocytes
- Treatment: remove offending drug, supportive treatment (electrolyte replacement, wound care, nutritional support, hydration) typically in ICU or burn unit

**Table 7-13 Duration Before Onset of Drug Reaction**

Reaction	Typical Onset of Eruption After Drug Ingestion
AGEP	Hours to 2 days
Phototoxic eruption	Hours to 7 days
Urticaria	Hours to 6 days
Lichenoid eruption	30–100 days
Fixed drug eruption	Up to 2 weeks with first exposure (<24 h in subsequent exposure)
DRESS	2–6 weeks (mean 3–4 weeks)
SJS/TEN	7–21 days (first 2 months for anticonvulsant)
Morbilliform reaction	7–21 days
LABD	24 h–2 weeks
Pemphigus vulgaris	Several weeks or months



**Figure 7.4**

**A:** Fixed drug eruption (Courtesy of Dr. Sophie M. Worobec)

**B:** Fixed drug eruption (Courtesy of Dr. Paul Getz)

**C:** Fixed drug eruption (Courtesy of Dr. Paul Getz)

**D:** Fixed drug eruption (bullous)

**E:** Acneiform eruption (due to EGFRi)

**F:** Flagellate pigmentation (bleomycin)

(Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. *Braun-Falco's Dermatology*. 3rd ed. Heidelberg: Springer; 2009)





**Figure 7.5**

**A:** Acneiform eruption (EGFRI)

**B:** Hydroxyurea ulceration

(Courtesy of Dr. Sophie M. Worobec)

**C:** Nail hyperpigmentation (AZT)

(Courtesy of Dr. Iris K. Aronson)

**D:** Toxic epidermal necrolysis

(Courtesy of Dr. Paul Getz)

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# 8

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## 8.1 STAINS

**Table 8-1 Histologic Stains for Specific Tissue**

Special Stain	Target	Color
<b>Collagen/Muscle</b>		
Masson trichrome	Collagen	Blue or green
	Muscle, nerves, nuclei	Dark red
Verhoeff-van Gieson	Collagen	Red
	Nuclei, muscles, and nerves	Yellow
Aldehyde fuchsin (Gomori)	Collagen	Red
Mallory triple stain or trichrome stain (aniline blue)	Collagen	Blue
	Muscle	Red
PTAH (phosphotungstic acid hematoxylin)	Collagen	Red
	Muscle/fibrin	Blue
Movat's pentachrome	Collagen	Yellow
	Muscle/fibrin	Red
<b>Elastic tissue</b>		
Verhoeff-van Gieson	Elastic fibers	Black
Orcein-Giemsa (Pinkus acid orcein)	Elastic fibers	Black
Aldehyde fuchsin (Gomori)	Elastic fibers	Blue or purple
Movat's pentachrome	Elastic fibers	Black
<b>Nerve</b>		
Bodian	Nerve fibers	Black
<b>Fat</b>		
Oil-red-O	Lipid	Red
Sudan black B	Lipid	Black
Scarlet red	Lipid	Red brown
<b>Melanin</b>		
Fontana-Masson	Melanin	Black
Orcein-Giemsa	Melanin	Brown-black
Silver nitrate	Melanin	Black
<b>Hemosiderin</b>		
Perls	Hemosiderin/iron (not melanin)	Bright blue
Prussian blue	Iron/hemosiderin	Blue
Turnbull's blue	Iron/hemosiderin	Blue
<b>Calcium</b>		
Alizarin Red S	Ca <sup>++</sup>	Reddish orange
Von Kossa	Ca <sup>++</sup>	Brown black
<b>Mucin/Mucopolysaccharides</b>		
Toluidine blue	Acid MPS	Purple
Alcian blue	Acid MPS (pH 2.5)	Blue
	Sulfated MPS (pH 0.5)	
Aldehyde fuchsin (Gomori)	Acid MPS, elastic tissue	Blue
Colloidal iron	Acid MPS	Blue

**Table 8-1 Histologic Stains for Specific Tissue (cont'd)**

Special Stain	Target	Color
Crystal violet	Acid MPS	Purple with blue background
Mucicarmine	“Epithelial” mucin	Bright pink ( <i>Paget’s, cryptococcus capsule</i> )
Giemsa	Acid MPS	Metachromatically purple
PAS	Neutral MPS	Pink
<b>Amyloid</b>		
Congo red	Amyloid	Pink-red, green birefringence with polarization
Crystal violet	Amyloid	Purple with blue background
Thioflavin T	Amyloid	Yellow fluorescence under fluorescent microscope
Scarlet red	Amyloid	Red
Orcein-Giemsa	Amyloid	Light blue
<b>Mast cells</b>		
Leder (chloroacetate esterase)	Granules	Red
Giemsa	Granules	Purple
Toluidine blue	Granules	Purple
Tryptase	Granules	Red to brown
<b>Bacteria</b>		
Gram stain	Gram-positive	Blue
	Gram-negative	Red
		Brown-Brenn and Brown-Hopps – modified gram stain
Fite	<i>M. leprae, Nocardia</i>	Red
Ziehl–Neelsen	Acid fast bacteria	Red
		Fite better than Ziehl–Neelsen for more delicate <i>M. leprae</i> bacilli
Warthin–Starry	Spirochetes	Black
Steiner	Spirochetes	Black
Giemsa	<i>Leishmania, Histoplasma, Rickettsia</i>	Purple to blue
<b>DNA/RNA</b>		
Methyl green-pyronin	RNA	Pink-red
	DNA	Blue-green
Feulgen	DNA only	Magenta
<b>Fungi</b>		
GMS (Gomori methenamine silver)	Donovan bodies, fungi	Black
PAS (Periodic acid-Schiff)	Fungi, neutral MPS, glycogen	Red
Grocott	Fungi	Fungus cell wall: black

**Table 8-2 Immunohistochemical Stains**

Marker	Normal Location in	Positive in
<b>Epithelial markers</b>		
<b>Cytokeratin</b> (Keratin)	Epithelial cells, $\pm$ sweat glands  Types of keratin: <u>AE1</u> (low molecular weight): basal epidermis, sweat glands <u>AE3</u> (high molecular weight): mid to superficial epidermis <u>CAM 5.2</u> : Paget's disease; <u>CK 7</u> : Paget's disease; <u>CK 20</u> : Merkel cell carcinoma	Epithelial tumors, some adnexal tumors
<b>Melanocytic</b>		
<b>S100</b>	Melanocytes, neural cells, smooth/skeletal muscle cells, Langerhans cells, eccrine and apocrine glands, chondrocytes	Langerhans cell histiocytosis, melanoma, granular cell tumor, eccrine neoplasms, neural tumors, liposarcoma
<b>HMB-45</b>	Melanocytes (less sensitive but more specific than S100)	Melanoma, some normal nevi, Spitz nevus, angiomyolipoma, breast carcinoma
Of note, <b>MART-1/Melan A</b> and <b>Mel-5</b> are comparable to HMB-45		
<b>Adnexal</b>		
<b>CEA</b> (Carcinoembryonic antigen)	Eccrine glands	Paget's disease, extramammary Paget's, epithelioid sarcoma (sometimes), sweat gland tumors, adenocarcinomas (gastric, lung, breast, etc.)
<b>EMA</b> (Epithelial membrane antigen)	Eccrine glands, some epithelial malignancies	Paget's disease, merkel cell carcinoma, meningioma, epithelioid sarcoma, most epithelial tumors
<b>Muscle</b>		
<b>Desmin</b>	Muscle cells (skeletal and smooth muscle)	Leiomyoma, leiomyosarcoma, glomus cell tumor (focally +), embryonal rhabdomyosarcoma
<b>Vimentin</b>	Muscle cells, fibroblasts, endothelial cells, histiocytes, lymphocytes, Schwann cells, melanocytes	Mesenchymal tumors (sarcomas, lymphomas, atypical fibroxanthoma, dermatofibrosarcoma protuberans), melanoma, glomus cell tumor
<b>Smooth muscle actin</b>	Myofibroblasts, muscle cells	Glomus tumors, smooth muscle tumors, some atypical fibroxanthomas
<b>Neural</b>		
<b>Neuron-specific enolase</b> (NSE)	Nonspecific neuroendocrine marker	Granular cell tumor, merkel cell carcinoma, other neuroendocrine tumors, some melanocytic tumors (melanoma), schwannoma
<b>Glial fibrillary acidic protein</b> (GFAP)	Glial cells, astrocytes, Schwann cells	Nerve sheath tumors
<b>Chromogranin</b>	Neuroendocrine neoplasms	Merkel cell carcinoma
<b>Synaptophysin</b>	Neuroendocrine neoplasms	Merkel cell carcinoma
<b>Myelin basic protein</b> (MBP)	Myelin sheath tissue, Schwann cells	Neurofibroma, neuroma, granular cell tumor
<b>Endothelial</b>		
<b>Factor VIII-related antigen</b> (von Willebrand)	Endothelial cells (not as sensitive as CD31)	Vascular tumors (both benign and malignant)
<b>CD31</b>	Monocytes, granulocytes, T/B cells, endothelial cells	Vascular neoplasms (angiosarcoma)
<b>Ulex europaeus agglutinin 1</b> (UEA)	Endothelial cells, most eccrine glands, keratinocytes	Vascular tumors
<b>CD34</b>	Endothelial cells, nerves, hematopoietic cells	Vascular tumors (benign/malignant), dermatofibrosarcoma protuberans, vascular tumors (not as sensitive as ulex), neurofibroma, epithelioid sarcoma, spindle cell lipoma, fibrous papule

**Table 8-2 Immunohistochemical Stains (cont'd)**

Marker	Normal Location in	Positive in
<b>Miscellaneous</b>		
<b>Factor XIIIa</b>	Macrophages, dermal dendrocytes, platelets	Dermatofibroma, xanthoma disseminatum, fibrous papule, AFX, xanthogranuloma
<b>Bcl-2</b>	Indicator of ↓ apoptosis, ↑ cell longevity	Follicular center cell lymphoma
<b>Gross Cystic Disease Fluid Protein 15</b> (GCDFP-15)	Apocrine glands	Apocrine tumors, breast carcinoma, salivary gland tumors

**Table 8-3 Specific Cells and Markers**

Cell type	Markers
<b>Macrophage</b>	α1-antitrypsin, lysozyme, HAM 56, CD 68
<b>Melanocyte</b>	S100, HMB 45, mart1/melanA, vimentin
<b>Langerhans cell</b>	S100, CD1a, vimentin
<b>Merkel cell</b>	CK20, neurofilament, chromogranin A, NSE, synaptophysin, ± EMA
<b>Sebaceous gland</b>	EMA, keratin
<b>Sweat gland</b>	CEA, EMA, keratin (cytoplasmic positivity), gross cystic disease fluid protein-15 (in apocrine and some eccrine), smooth muscle actin (in myoepithelial cells)
<b>Fibroblast</b>	Vimentin
<b>Mast cell</b>	CD117 (c-kit)
<b>Myofibroblast</b>	Muscle-specific actin, desmin (sometimes)
<b>Dermal dendrocytes</b>	Factor XIIIa
<b>Blood vessels</b>	Factor VIII–related Ag, CD31, CD34, vimentin
<b>Nerves</b>	Axons: neurofilament, NSE
	Schwann cells: S100, GFAP, myelin basic protein (MBP)
<b>Muscle</b>	Smooth muscle actin

**Table 8-4 Specific Tumors and Respective Markers**

Entity	Positive Markers	Negative Markers
<b>Atypical fibroxanthoma</b> (AFX)	Vimentin, actin, + histiocyte stains (i.e., CD68)	S100, pankeratin, CD34, CEA, EMA, desmin
<b>Leiomyosarcoma</b>	Desmin, smooth muscle actin, ± vimentin	CEA, S100 (only rarely positive), keratin (only rarely positive)
<b>Melanoma</b>	S100, vimentin, melanA, HMB45 (latter negative in desmoplastic/spindle cell melanoma)	Keratin CD45 (also known as leukocyte common antigen or LCA), CEA, EMA, desmin
<b>Angiosarcoma</b>	CD31, CD34, Factor VIII–related antigen, Ulex europaeus	Keratin, CEA, EMA, S100
<b>Merkel cell carcinoma</b> (MCC)	CK 20, EMA, NSE, synaptophysin, chromogranin	S100, CD45, CEA, vimentin, desmin, GFAP, thyroid transcription factor-1 or TTF-1
<b>Schwannoma</b> (Neurilemmoma)	Vimentin, S100, MBP	Keratin, neurofilaments, desmin
<b>Glomus tumor</b>	Vimentin, smooth muscle actin	Desmin (occasionally focally positive), cytokeratin
<b>Epithelioid sarcoma</b>	Cytokeratin, CD34 (50% cases), EMA, vimentin, ± CEA	

*Continued on the next page*



**Table 8-4 Specific Tumors and Respective Markers (cont'd)**

Entity	Positive Markers	Negative Markers
<b>DFSP</b>	Vimentin, <b>CD34</b>	S100, HMB45, keratin, <b>stromelysin-3, Factor XIIIa</b> (latter two markers positive in dermatofibroma)
<b>Paget's disease</b>	CK7, EMA, CEA, GCDFP-15	S100, HMB45
<b>Sebaceous carcinoma</b>	EMA, keratin (CAM 5.2)	CEA (usually), S100
<b>Granular cell tumor</b>	S100, NSE, MBP	GFAP, neurofilament

**Table 8-5 Markers for Different Tumors**

Tumor	Keratin	S100	Vimentin	Actin	CD31	CD34	CD45	CD68
<b>Carcinoma</b>	+	–	–	–	–	–	–	–
<b>Fibrohistiocytic</b>	–	–	+	+/-	–	+/-	–	+
<b>Sarcoma</b>	–	–	+	+/-	+/-	+/-	–	–
<b>Angiosarcoma</b>	–	–	+	–	+	+	–	–
<b>Melanoma</b>	–	+	+	–	–	–	–	–
<b>Lymphoma</b>	–	–	+/-	–	–	–	+	–
<b>Muscle</b>	–	–	+	+	–	–	–	–
<b>Nerve</b>	–	+	+	–	–	+	–	–

**Table 8-6 Differential Diagnosis of Spindle Cell Tumors**

Entity	Keratin	S100	Factor VIII	HMB-45	Desmin	Vimentin
<b>SCC</b>	+	–	–	–	–	–
<b>Atypical fibroxanthoma</b>	–	–	–	–	–	+
<b>Melanoma</b>	–	+	–	+	–	+
<b>Leiomyosarcoma</b>	–	–	–	–	+	+
<b>Angiosarcoma</b>	–	–	+	–	–	–

**Table 8-7 Differential Diagnosis for Small Blue Cells**

Entity	Keratin	LCA (CD45)	S-100	Synaptophysin
<b>MCC</b>	+	–	–	+
<b>Lymphoma</b>	–	+	–	–
<b>Carcinoma</b>	+	–	+/-	–
<b>Melanoma</b>	–	–	+	–

**Table 8-8 Differential Diagnosis for Pagetoid Cells**

Marker	Paget's Disease	Extramammary Paget's Disease	Pagetoid Spread of Melanoma	Pagetoid Bowen's Disease
<b>Cytokeratin (AE1/AE3)</b>	+	+	–	+/-
<b>CAM 5.2</b>	+	+	–	+/-
<b>CK7</b>	+	+	–	–
<b>EMA</b>	+	+	–	–
<b>CEA</b>	+	+	–	–

**Table 8-8 Differential Diagnosis for Pagetoid Cells (cont'd)**

Marker	Paget's Disease	Extramammary Paget's Disease	Pagetoid Spread of Melanoma	Pagetoid Bowen's Disease
<b>S100</b>	–	–	+	–
<b>HMB45</b>	–	–	+	–
<b>CGDFP-15</b>	+	+	–	–

## 8.2 HISTOLOGIC BODIES

**Table 8-9 Characteristic Histologic Bodies**

Histologic Body	Description	Entity
Antoni A tissue	Cellular pattern ( <i>spindle cells arranged in stacks with palisading nuclei</i> ) with Verocay bodies	Schwannoma
Antoni B tissue	Hypocellular pattern: loose stroma and few cells	Schwannoma
Asteroid bodies	Extracellular central spore surrounded by radiating homogenous eosinophilic material	Sporotrichosis ( <i>Splendore-Hoepli phenomenon</i> )
	Intracellular stellate eosinophilic inclusion bodies within multinucleated giant cell	Sarcoidosis, berylliosis, foreign body reaction, etc.
Banana bodies	Banana-shaped golden-yellow ( <i>ochre</i> ) fibers	Ochronosis
Bean bag cells	Histiocytes showing phagocytosis of lymphocytes, erythrocytes, or platelets	Cytophagic histiocytic panniculitis
Birbeck granules	Tennis racket-shaped or rod-shaped structures within cytoplasm of Langerhans cell seen on EM	Langerhans cell histiocytosis
Caterpillar bodies	Wavy eosinophilic material in basal epidermal layer or roof of blister	Porphyria cutanea tarda, erythropoietic porphyria
Cholesterol clefts	Lipid crystals inside adipocytes forming rosettes of needle-like clefts	Sclerema neonatorum, subcutaneous fat necrosis of newborn
	Clear needle-shaped spaces ( <i>not necessarily in adipocytes</i> )	Xanthomas, necrobiotic xanthogranuloma
Colloid bodies (Civatte bodies)	Eosinophilic homogenous structures ( <i>cell remnants</i> ) in lower epidermis or papillary dermis	Lichen planus, other interface dermatoses
Corp ronds	Dyskeratotic acantholytic keratinocytes with round nuclei and perinuclear halo	Darier's disease, Hailey-Hailey, Grover's disease, warty dyskeratoma
Cowdry Type A inclusion bodies	Large eosinophilic intranuclear inclusion with surrounding clear halo in infected cells	HSV and VZV infection
Cowdry Type B inclusion bodies	Intranuclear amorphous bodies surrounded by clear halo in neural cells	Polio
Donovan bodies	Intracytoplasmic bacteria in infected histiocytes ( <i>vacuolated appearance containing bacilli</i> )	Granuloma inguinale
Dutcher bodies	Eosinophilic intranuclear inclusions of immunoglobulins in malignant plasma cells	Multiple myeloma
Flame figures	Eosinophilic material ( <i>cells and debris</i> ) surrounding pink amorphous collagen	Well's syndrome, arthropod bite, drug reaction
Floret-type giant cell	Giant cells with eosinophilic cytoplasm and marginally placed nuclei resembling small flower	Pleomorphic lipoma
Globi	Foamy histiocytes containing clustered bacilli	Lepromatous leprosy

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**Table 8-9 Characteristic Histologic Bodies (cont'd)**

Histologic Body	Description	Entity
Gamma Favre body	Large intracytoplasmic basophilic inclusion body	Lymphogranuloma venereum
Gargoyle cells	Fibroblast with large deposits of mucopolysaccharide (MPS)	MPS storage diseases (i.e., Hurler)
Grains	Basophilic dyskeratotic cells with elongated wavy or “grain-shaped” nuclei in granular layer	Darier’s disease, Hailey-Hailey, Grover’s disease, warty dyskeratoma
Guarnieri bodies	Eosinophilic cytoplasmic inclusions in affected epithelial cells	Vaccinia or smallpox
Henderson-Patterson bodies	Large eosinophilic cytoplasmic inclusion of viral protein in keratinocytes	Molluscum contagiosum
Kamino bodies	Eosinophilic amorphous globules ( <i>contain basement membrane component</i> )	Spitz nevi
Koilocytes	Keratinocyte with hyperchromatic nuclei surrounded by perinuclear halo	HPV infection
Langhans giant cells	Multinucleated giant cell with nuclei arranged peripherally in a horseshoe-shaped pattern (unlike foreign body giant cells with haphazard pattern)	Sarcoidosis, tuberculosis
Lipofuscin granules	Lipofuscin yellow-brown granule accumulation in dermal macrophages	Amiodarone pigmentation
Max Joseph space	Artifactual clefting at dermo-epidermal junction	Lichen planus
Medlar bodies (Copper pennies)	Thick-walled spherical brown cells	Chromomycosis
Miescher’s radial granuloma	Nodules containing histiocytes arranged radially around central cleft in interlobular septae	Erythema nodosum
Miescher’s granuloma	Phagocytosis of dermal elastic fibers by giant cells and histiocytes	Annular elastolytic giant cell granuloma ( <i>actinic granuloma</i> )
Michaelis Gutmann bodies	Concentric basophilic lamellar bodies in foamy macrophages ( <i>von Hanseman</i> ) in urinary tract	Malakoplakia
Mikulicz cell	Foamy macrophage containing bacilli	Rhinoscleroma
Mariner’s wheel	Budding yeast resemble “mariner’s wheel”	Paracoccidioidomycosis
Mulberry cells	Multiple septations with mulberry-like sporangia	Protothecosis, hibernoma
Munro microabscess	Small collection of neutrophils within horny layer associated with parakeratosis	Psoriasis
Negri bodies	Neuronal eosinophilic bodies	Rabies
Pautrier microabscesses	Collection of atypical T cells within epidermis	Cutaneous T-cell lymphoma
Psammoma body	Concentrically laminated collection of calcium	Meningioma
Pustulo-ovoid bodies	Round eosinophilic cytoplasmic inclusion	Granular cell tumor
Rocha-Lima bodies	Pink-purple cytoplasmic inclusion in endothelial cells	Oroya fever/verruca peruana
Russell bodies	Eosinophilic immunoglobulin deposits within plasma cell	Rhinoscleroma, granuloma inguinale
Verocay body	Parallel rows of nuclei surrounded by homogenous eosinophilic material	Schwannoma
Schaumann bodies	Calcified inclusion from degenerated lysosomes in macrophages	Sarcoidosis
Virchow cells	Foamy histiocytes containing <i>M. leprae</i>	Lepromatous leprosy
Von Hanseman cells	Foamy eosinophilic macrophages containing Michaelis Gutmann bodies	Malakoplakia

**Table 8-10 Characteristic Histologic Findings**

Histopathologic Finding	Seen in:
<b>Cornified Layer</b>	
Follicular plugging	Pityriasis rubra pilaris (PRP), lichen planopilaris (LPP), lichen sclerosus, lupus erythematosus (LE), perforating folliculitis
Cornoid lamella	Porokeratosis
Compact parakeratosis with retained KHG	Axillary granular parakeratosis
“Checkerboard” and “shoulder” parakeratosis	PRP
Mounds of parakeratosis	Psoriasis
Focal parakeratosis	Guttate psoriasis, pityriasis rosea, pityriasis lichenoides
Confluent parakeratosis	Psoriasis, Bowen’s disease, necrolytic migratory erythema (NEM) in glucagonoma syndrome
Columns of parakeratosis	Verruca vulgaris (VV), porokeratosis
Alternating parakeratosis	Actinic keratosis (AK)
Sandwich parakeratosis	Tinea
Confluent hyperkeratosis	Lichen planus (LP)
Massive orthokeratosis	Acquired digital fibrokeratoma
“Church spire” papillomatosis	Acrokeratosis verruciformis
Papillomatosis	Acanthosis nigricans, VV, seborrheic keratosis (SK), acrochordon
Neutrophils in crust	Candidiasis, psoriasis, impetigo, tinea, syphilis
Munro microabscess in cornified layer	Psoriasis (plate-like neutrophils in multilayered scale)
<b>Epidermis</b>	
“Claw” ( <i>epidermis</i> ) clutching a “ball” ( <i>dermis</i> )	Lichen nitidus
Epidermal necrosis	Herpes simplex (HSV) infection, toxic epidermal necrolysis, erythema multiforme (EM), NEM, hydroa vacciniforme, graft-versus-host disease (GVHD), acute fixed drug reaction (FDE)
Atrophic epidermis	Porokeratosis, atrophic AK, radiation dermatitis, lichen sclerosus, LE, dermatomyositis, poikiloderma, necrobiosis lipoidica, GVHD
Upper pallor with normal-appearing lower epidermis	NEM, ± acrodermatitis enteropathica
Windblown appearance	Bowen’s disease
Subcorneal/intragranular split with acantholytic cells (cling on)	Pemphigus foliaceus ( <i>sometimes can look like impetigo if neutrophils within blister cavity</i> )
Eosinophilic spongiosis ( <i>hAPPIE</i> )	Arthropod bite, pemphigoid, pemphigus, incontinentia pigmenti (IP), eruption (drug), contact dermatitis
Foam cells in epidermis	Balloon cell nevus
Dyskeratotic or necrotic keratinocytes	EM, pityriasis lichenoides et varioliformis acuta (PLEVA), paraneoplastic pemphigus, acrodermatitis enteropathica, acute FDE, IP, NEM, GVHD, radiation dermatitis
Vacuolated keratinocytes ( <i>empty shells</i> )	Tissue-processing artifact, freezing artifact, epidermolytic hyperkeratosis
Elongated keratinocytes	Electrodessication artifact
Acantholytic cells	Darier’s disease, Hailey-Hailey disease, HSV infection, transient acantholytic dermatosis (Grover’s disease), pemphigus ( <i>acantholysis involves hair follicles</i> ), warty dyskeratoma, acantholytic SCC or AK
Koilocytes	HPV infection
Multinucleated keratinocytes	HSV ( <i>steel gray nuclei</i> )
Epidermotropic lymphocytes	Cutaneous T-cell lymphoma (CTCL)
Pagetoid cells	Bowen’s disease, melanoma, recurrent nevus, Paget’s disease, CTCL, lymphomatoid papulomatosis (LyP), Langerhans cell histiocytosis (LCH)
Dilapidated brick wall	Hailey-Hailey disease

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**Table 8-10 Characteristic Histologic Findings (cont'd)**

Histopathologic Finding	Seen in:
<b>Epidermis (cont'd)</b>	
Pautrier microabscesses	CTCL
Tombstoning of basal cells	Pemphigus vulgaris
Clumped keratohyaline granules (KHG)	Epidermolytic hyperkeratosis, verruca (HPV infection)
Squamous eddies	Irritated seborrheic keratosis (SK), inverted follicular keratosis (IFK), SCC, trichoblastoma
Horn pseudocysts	SK, IFK, trichoepithelioma, microcystic adnexal carcinoma
Basilar hyperpigmentation	Dermatofibroma, SK, acanthosis nigricans
Flattened ( <i>tabled</i> ) rete ridges	Dermatofibroma
“Saw-toothed” rete ridges	LP
Vacuolar interface change	LE, LP, GVHD, dermatomyositis, acute FDE, lichen nitidus, erythema dyschromicum perstans (ashy dermatosis), lichenoid keratosis, lichen sclerosus, EM, PLEVA
<b>Dermis</b>	
Thick basement membrane	LE
Grenz zone	Lepromatous leprosy, granuloma faciale, lymphocytoma cutis ( <i>bottom heavy</i> ), leukemia cutis ( <i>top heavy</i> )
Subtle amorphous pink deposits in papillary dermis	Macular amyloidosis
Band-like lymphocytic infiltrate	LP, EM, lichen sclerosus, benign lichenoid keratosis, lichen striatus, halo nevus
Upper dermal edema	Polymorphous light eruption (PMLE), Sweet’s syndrome, lichen sclerosus, langerhans cell histiocytosis
Melanin incontinence	Macular amyloidosis, LE, atrophic LP, ashy dermatosis, FDE, dermatomyositis, postinflammatory hyperpigmentation, ± IP
Subepidermal split with prominent eosinophils	Bullous pemphigoid, pemphigoid gestationis, bullous drug eruption
Subepidermal split with prominent neutrophils	Dermatitis herpetiformis, bullous SLE, linear IgA bullous disease (LABD)
Neutrophils in dermal papillae	Dermatitis herpetiformis
Subepidermal split with prominent lymphocytes	Bullous LP, PMLE, lichen sclerosus
Subepidermal vesicles with scant inflammation	Porphyria cutanea tarda (PCT)
Subepidermal vesicles with mast cells	Bullous mastocytosis
Fibrous stroma	Syringoma, trichoepithelioma, morpheaform BCC, microcystic adnexal carcinoma
“Bubble gum” pink stroma	Neurofibroma
Lymphocytes around sweat glands	Lichen striatus
Sweat glands with neutrophils	Neutrophilic eccrine hidradenitis
Necrosis of sweat glands	Coma blister
Invaginated pilosebaceous unit with dark-staining ducts	Supernumerary nipple
Extravasated red blood cells	Pityriasis rosea, PLEVA, stasis dermatitis, pigmented purpuric dermatoses, vascular neoplasms, vasculitis, granuloma faciale (GF)
Hemosiderin	Hemochromatosis, pigmented purpuric dermatosis, stasis dermatitis, GF, pityriasis lichenoides, vascular neoplasms, vasculitis
Vertically oriented collagen	Acquired digital fibrokeratoma
Collagen trapping at periphery	Dermatofibroma
Keloidal collagen	Dermatofibroma, keloid
Necrobiosis	Granuloma annulare (GA), necrobiosis lipoidica diabetorum (NLD), rheumatoid nodule, necrobiotic xanthogranuloma (NXG)

**Table 8-10 Characteristic Histologic Findings (cont'd)**

Histopathologic Finding	Seen in:
<b>Dermis (cont'd)</b>	
Horizontal “sandwich” necrobiosis without palisading	NLD
Dermal fibrosis	Angiofibroma, fibrous papule, hypertrophic scar, blue nevus, keloid, radiotherapy, morpheaform BCC, desmoplastic trichoepithelioma, syringoma
Dermal necrosis	Epithelioid sarcoma, malignant atrophic papulosis (Degos)
Clumped calcified elastic fibers	Pseudoxanthoma elasticum (PXE)
Vasculitis	GF, erythema elevatum diutinum (EED), polyarteritis nodosa (PAN), Henoch-Schonlein purpura, urticarial vasculitis, acute hemorrhagic edema of infancy
Nuclear dust	Sweet’s syndrome, leukocytoclastic vasculitis, GF, PAN, pyoderma gangrenosum (PG)
Deep pink nodules	Nodular amyloidosis
Smooth muscle bundles	Supernumerary nipple, leiomyoma ( <i>fascicles and bundles</i> )
Calcification	Pilomatricoma, PXE, calciphylaxis, osteoma cutis, cysts, panniculitis, calcinosis cutis, subepidermal calcified nodule
Increased mucin deposition	LE, dermatomyositis, scleromyxedema, scleredema diabeticorum, BCC ( <i>some</i> ), mucopolysaccharidosis, reticular erythematous mucinosis, GA ( <i>not NLD</i> ), pretibial myxedema, focal mucinosis, follicular mucinosis
Pool of mucin	Myxoid cyst, mucocoele, focal cutaneous mucinosis, mucinous carcinoma
Ductal cells floating in mucin	Eccrine mucinous carcinoma
Tadpole-shaped ducts	Syringoma
Extracellular pool of lipid	Eruptive xanthoma
Empty vacuoles in dermis and epidermis	Freeze artifact
Pink to purple reticular network in dermis	Gel foam artifact
Drag marks	Cutting artifact ( <i>knife mark artifact</i> )
Tiny black particles around blood vessels	Argyria
Black amorphous deposits around blood vessels	Lead tattoo
Tiny wispy gold to black granules in mouth	Amalgam tattoo
Nerve bundles	Amputation neuroma, supernumerary digit
Stromal retraction	BCC
Basaloid islands ( <i>jigsaw puzzle</i> )	Cylindroma
“Cluster of grapes” ( <i>low power</i> )	Merkel cell carcinoma
Hyalinized droplets	Cylindroma
Cannon or blue balls in dermis	Eccrine spiradenoma
Circular basaloid rosettes	Eccrine spiradenoma
Spindle and epithelioid melanocytes “raining” down	Spitz nevus
<b>Inflammatory Infiltrate</b>	
Lichenoid infiltrate	LP, lichenoid drug eruption, lichen sclerosus, secondary syphilis ( <i>with plasma cells</i> ), GVHD, pityriasis lichenoides, lichen striatus, CTCL
Interstitial dermatitis	GA, Well’s syndrome, Sweet’s syndrome, interstitial drug reaction, urticaria
Coat-sleeving or perivascular cuffing of lymphocytes	Erythema annulare centrifugum ( <i>no epidermal change</i> )

*Continued on the next page*

**Table 8-10 Characteristic Histologic Findings (cont'd)**

Histopathologic Finding	Seen in:
<b>Inflammatory Infiltrate (cont'd)</b>	
Superficial and deep lymphocytic infiltrate	PMLE, secondary syphilis, gyrate erythemas, athropod bites, LE ( <i>latter includes periadnexal infiltrate</i> )
Deep infiltrate around sweat glands	Lichen striatus
“Naked” granulomas	Sarcoidosis, tuberculosis, tuberculoid leprosy
Single filing or “indian” filing of cells	GA, congenital melanocytic nevus, lymphoma, leukemia, glomus cell tumor, metastatic breast carcinoma
Increased mast cells	Urticaria, neural tumors (i.e., <i>neurofibroma</i> ), mucinous areas
Increased plasma cells	Mucous membrane ( <i>normal</i> ), secondary syphilis, syringocystadenoma papilliferum, hidradenitis suppurativa, acne keloidalis nuchae, NLD, LE, Rosai–Dorfman disease
<b>Cells in Dermis</b>	
Basaloid cells	BCC, SK (reticulated variant), trichoepithelioma, eccrine tumors
Diffuse dermal mast cells	Mastocytosis (i.e., <i>urticaria pigmentosa</i> )
Cells with reniform nuclei	Langerhans cell histiocytosis ( <i>abundant pale cytoplasm</i> )
Spindle-shaped cells with elongated, wavy nuclei	Neurofibroma
Round monotonous cells	Glomus cell tumor, poroma, mastocytosis ( <i>blue-purple granules</i> )
Pink granular cytoplasm	Granular cell tumor
Clear cells	Clear cell acanthoma, trichilemmoma, clear cell hidradenoma, metastatic renal cell carcinoma, clear cell SCC, balloon cell nevus, Paget’s disease, clear cell syringoma, eccrine carcinoma
Small cells	Lymphocytoma cutis, cutaneous B-cell lymphoma, metastatic small cell carcinoma, CTCL, Merkel cell carcinoma
Foamy macrophages	Xanthomas ( <i>eruptive, tuberous, tendinous, planar</i> ), verruciform xanthoma, xanthelasma, xanthoma disseminatum, atypical fibroxanthoma (AFX), juvenile xanthogranuloma (JXG), necrobiotic xanthogranuloma (NXG), leprosy, pancreatic panniculitis
Touton giant cell	Xanthelasma, AFX, NXG
Ground glass giant cell	Multicentric reticulohistiocytosis, reticulohistiocytic granuloma
Purple osteoclast-like giant cell	Giant cell tumor of tendon sheath, malignant fibrous histiocytoma
Bizarre multinucleated giant cell	Malignant fibrous histiocytoma, pleomorphic lipoma
Parasitized histiocytes <b>His GiRL</b>	<b>H</b> istoplasmosis, <b>g</b> ranuloma <b>i</b> nguinal, <b>r</b> hinoscleroma, <b>l</b> eishmaniasis
Ghost cells	Pilomatricoma
Fibroblast with red inclusion body	Infantile digital fibromatosis
Bizarre spindle cells	Liposarcoma, leiomyosarcoma, AFX, radiation dermatitis
<b>Hair</b>	
Melanin clumps ( <i>casts</i> ) in follicle	Trichotillomania
Trichomalacia ( <i>deformed shaft</i> )	Trichotillomania
Necrosis of hair follicles	HSV
Tiny vellus hairs	Accessory tragus ( <i>rim periphery</i> ), xanthelasma, vellus hair cyst
“Swarm of bees” ( <i>lymphocytic inflammation at hair bulb</i> )	Alopecia areata
Lymphocytes and plasma cells around follicles	Acne keloidalis nuchae
Free hair shafts surrounded by multinucleated giant cells	Acne keloidalis nuchae, folliculitis decalvans
Eosinophils around hair follicle	Eosinophilic folliculitis
Mucin within follicle	Follicular mucinosis

**Table 8-10 Characteristic Histologic Findings (cont'd)**

Histopathologic Finding	Seen in:
<b>Cartilage</b>	
Cartilage often present	Accessory tragus, chondrodermatitis nodularis helices (CNH), chondroid syringoma
Degenerated cartilage	Relapsing polychondritis, CNH
<b>Fat</b>	
Ghost-like fat cells	Pancreatic panniculitis ( <i>with basophilic calcium deposition</i> )
Cystic spaces in fat	Cold panniculitis
Fat necrosis	Erythema induratum ( <i>basophilic</i> ), lupus panniculitis ( <i>latter with lymphoid follicle-like aggregates, lymphoplasmacytic infiltrate</i> )
“Needle-shaped” clefts in fat	Subcutaneous fat necrosis, sclerema neonatorum, post-steroid panniculitis
Swiss cheese appearance	Paraffinoma or sclerosing lipogranuloma
Fat high up in lesion	Accessory tragus
Widened septae with giant cells	Erythema nodosum
Dense neutrophilic inflammation	$\alpha$ -1-antitrypsin deficiency
Lipomembranous changes	Lipodermatosclerosis
Chicken wire pattern ( <i>linear collapsed vessels</i> )	Myxoid liposarcoma
Clear multivacuolated cells in fat	Hibernoma
<b>Vessels</b>	
Hyalinized vessel walls ( <i>with thick red color around vessels</i> )	Atrophie blanche
Promontory sign, slit-like spaces	Kaposi sarcoma
Atypical endothelial cells with dissecting vascular spaces	Angiosarcoma
Intravascular thrombi	Cryoglobulinemia, purpura fulminans, antiphospholipid syndrome, disseminated intravascular coagulation, coumadin necrosis, atrophie blanche
Telangiectatic vessels in pale acellular dermis	Radiation dermatitis
Hob nailing ( <i>endothelial cells protrude into vessel</i> )	Angiolymphoid hyperplasia with eosinophilia
Staghorn appearance	Hemangiopericytoma
Recanalizing thrombus	Masson's tumor (intravascular endothelial hyperplasia)
Spindle cells with RBCs “sandwiched” in between	Kaposi sarcoma
Polypoid collection of vessels	Pyogenic granuloma
Proliferation of thick-walled vessels with hemosiderin	Stasis dermatitis
Dilated engorged vessels with surrounding edema	Granulation tissue



### 8.3 HISTOPATHOLOGIC FINDINGS

**Table 8-11 Differential Diagnosis**

Finding	Seen in:
Deep lesion (no epidermis/upper dermis seen)	Rheumatoid nodule, malignant fibrous histiocytoma, neurothekeoma, paraffinoma, giant cell tumor of tendon sheath, nodular fasciitis, myxoid liposarcoma, angioliipoma, angioleiomyoma, $\pm$ neurilemmoma, gout, hibernoma
Painful tumors: <b>BLEND AN EGG</b>	Blue rubber bleb, leiomyoma, eccrine spiradenoma, neurilemmoma, dermatofibroma, angioliipoma, neuroma, erythema nodosum, endometriosis, glomus tumor, glomangioma
Polypoid	Accessory tragus, digital fibrokeratoma
Acral	Digital fibrokeratoma, verruca, supernumerary digit, amputation neuroma, myoid cyst
Minimal change	Tinea versicolor, macular amyloidosis, ichthyosis vulgaris, telangiectasia macularis eruptiva perstans, vitiligo, urticaria
Squared off ( <i>boxcar</i> ) biopsy	Scleredema, pretibial myxedema, morphea, advanced NLD

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# 9

## Dermoscopy and Electron Microscopy

### Contents

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## 9.1 DERMOSCOPY

- Also known as skin surface microscopy, dermatoscopy, and/or epiluminescence microscopy
- Pigmentation in lesion due to either melanin or hemoglobin (vasculature)
- Melanin may be found within melanocytes, keratinocytes, melanophages, or sequestered tumor cells (i.e., pigmented BCC); color depends on depth of melanin in skin
  - Black color: melanin within stratum corneum or upper epidermis
  - Brown color: melanin at dermoepidermal junction
  - Gray or blue color: melanin within dermis
- Location-specific features
  - Face: follicular openings may create pseudonetwork (follicular openings form hypopigmented “holes” of network)
  - Volar: nevi on palmoplantar skin with different pattern than other areas of the body; most common is parallel furrow pattern followed by lattice-like and fibrillar pattern

**Table 9-1 Patterns in Benign Lesions**

Feature	Description	Associated with
<b>Patterns in Melanocytic Nevi</b>		
<b>Reticular pattern</b> (Figure 9.1A) (most common)	Pigment network characterized by a grid of thin brown lines with hypopigmented “holes” (honeycomb-like pattern)	Benign acquired melanocytic nevi, lentigo simplex, solar lentigo, sometimes seen in melanoma
<b>Globular pattern</b> (Figure 9.1B)	Various sized brown to gray-black round to oval structures	Acquired melanocytic nevi, congenital nevi
<b>Cobblestone pattern</b>	Similar to globular but closely aggregated angulated globules	Papillomatous dermal nevi, congenital nevi
<b>Homogenous pattern</b> (Figure 9.1D)	Diffuse, uniform, and structureless areas ranging from brown, gray-blue to gray-black (no pigment network)	Blue nevus (hallmark), ± intradermal nevus, can be seen in metastatic melanoma
<b>Starburst pattern</b>	Pigmented streaks in radial arrangement surrounding entire periphery of lesion	Spitz nevus
<b>Patterns in Acral-Specific Nevi</b>		
<b>Parallel furrow pattern</b> (Figure 9.1C)	Found exclusively in glabrous skin (palm/sole), parallel pigmented lines <b>within sulci or furrows</b> of glabrous skin and whitish dots (acrosyringia) between sulci (within ridges)	Acral benign melanocytic nevi  Of note, acral melanoma with <b>parallel ridge pattern</b>
<b>Lattice-like pattern</b>	Rectangular network of brown lines and several whitish dots	Acral benign melanocytic nevi
<b>Fibrillar pattern</b>	Several short and thin brown lines with parallel arrangement but also run oblique to the ridges/furrows of glabrous skin	Acral benign melanocytic nevi
<b>Patterns in Dermatofibromas</b>		
<b>Central white area</b> (Figure 9.2A, B)	Well-circumscribed milky white area in center of firm papule	
<b>Reticular network</b> (Figure 9.2A, B)	Often delicate, pale network seen at periphery	
<b>Patterns in Seborrheic Keratoses</b>		
<b>Moth-eaten border</b>	Punched out concave areas at periphery of lesion; also seen in ephelis, lentigo, and lentigo maligna	
<b>Fissures and crypts</b>	Irregular filled craters (crypts), irregular linear keratin-filled depressions	
<b>Comedo-like openings</b> (Figure 9.2C, D)	Brownish-yellow or brown-black structures with varying sizes; represents keratin plugs within dilated follicular openings (rarely can be seen in papillomatous dermal nevi)	
<b>Milia-like cysts</b> (Figure 9.2C, D)	White or yellowish discrete round structures of varying sizes; represents intraepidermal horn pseudocysts (can also be seen in papillomatous dermal nevi, rarely in melanoma)	

*Continued on the next page*

**Table 9-1 Patterns in Benign Lesions (cont'd)**

Feature	Description	Associated with
<b>Patterns in Seborrheic Keratoses (cont'd)</b>		
<b>Fingerprint-like structure</b>	Light brown curvilinear lines resembling fingerprints; found in early seborrheic keratosis and solar lentigo	
<b>Pattern in Vascular Lesions (hemangioma, angiokeratoma)</b>		
<b>Red-blue lacuna</b> (Figure 9.3C, D)	Sharply demarcated oval to round structures with varying shades (red, dark red, red-blue, to black); represents dilated vascular spaces in upper dermis (if dark red to black may be partially thrombosed)	

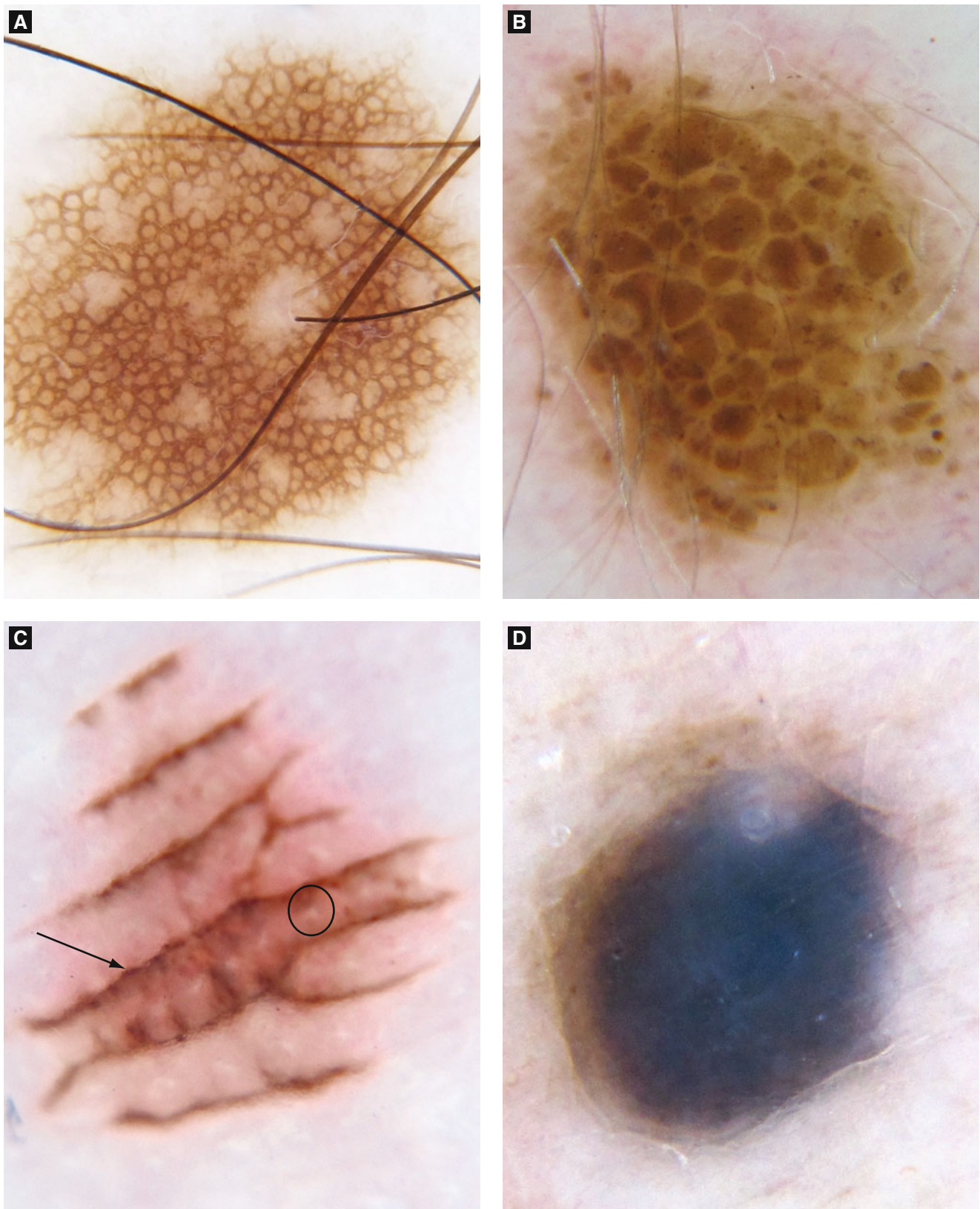
**Table 9-2 Vascular Patterns**

Feature	Description	Associated with
<b>Erythema</b>	Diffuse ill-defined pink-red area	Irritated lesions, dysplastic nevi, melanoma
<b>Milky red areas</b>	Red area with milky ground glass appearance	Amelanotic or hypomelanotic melanoma
<b>Various pink shades</b>	More than one shade of pink within lesion	Amelanotic or hypomelanotic melanoma
<b>Telangiectasias</b>	Can appear dilated and linear	BCCs (often arborizing), amelanotic melanoma (especially if central position)
<b>Pinpoint vessels</b>	Dot-like vessels	Melanocytic lesions (nevi and melanoma)
<b>Glomerular vessels</b>	Vessels resembling capillaries of renal glomerulus	Bowen's disease, psoriasis, clear cell acanthoma
<b>Comma vessels</b>	Comma-shaped vessels	Nevi (dermal and congenital), rarely amelanotic melanoma
<b>Linear irregular vessels</b>	Irregular-shaped wave-like vessels	Melanoma (especially if in combination with dotted vessels)
<b>Hair pin vessels</b>	Twisted loop appearance	Seborrheic keratosis, keratoacanthoma, squamous cell carcinoma
<b>Crown vessels</b>	Bending, orderly vessels which disappear in center of lesion	Sebaceous hyperplasia
<b>Corkscrew vessels</b>	Winding vessels with corkscrew appearance	Melanoma (cutaneous metastasis)
<b>Red-blue lacuna</b>	Well-defined ovoid red, red-blue, or black structures	Hemangiomas, angiokeratoma, or thrombosed hemangioma (if black structures)



**Table 9-3 Patterns in Malignant Lesions**

<b>Melanoma</b>	
<b>Atypical pigment network</b> (Figure 9.4C)	Thickened line segments (broad-width cords) with irregular width size, irregular distribution, and/or abrupt cutoff of atypical network at periphery
<b>Blue-white veil</b> (Figure 9.4D)	Overlying blue-white haze or ground glass film over focal areas of lesion due to large melanin-containing areas in upper dermis (such as confluent nests of heavily pigmented melanocytes or melanophages); not associated with red-blue lacunes
<b>Scar-like depigmentation</b>	White scar-like areas representing areas of regression
<b>Radial streaming</b>	Radial parallel linear extensions with asymmetric arrangement at periphery of lesion; can represent radial growth phase of melanoma
<b>Pseudopods</b>	Curved finger-like dark brown to black projections at periphery of lesion, appear irregular in distribution or focally at edge of lesion; never appear around entire circumference (like starburst pattern in Spitz nevus); may represent radial growth phase of melanoma
<b>Irregular streaks</b>	Dark, linear structures with variable thickness at periphery of lesion; represent heavily pigmented junctional nests of atypical melanocytes
<b>Irregular dots and globules</b>	Sharply circumscribed pigmented structures with either irregular shape or distribution; represents aggregation of pigmented melanocytes, melanophages, or even “clumps” of melanin
<b>Irregular blotches</b>	Various shades of diffuse hyperpigmentation obscuring underlying pattern (i.e., pigment network) with irregular shape; dissimilar structures that share melanin pigmentation through epidermis and upper dermis
<b>Rhomboidal structures</b>	Rhomboidal-shaped gray-brown structures often seen in lentigo maligna
<b>Irregular follicular pigmentation</b>	Asymmetric dark pigmentation around follicular openings; seen mainly in lentigo maligna
<b>Negative pigment network</b>	Light areas making up lines (cords) with dark “holes”; seen in Spitz nevi, dysplastic nevi, and melanoma
<b>Parallel ridge pattern</b>	Brown-gray thickened lines within <b>ridges</b> of the skin ( <b>white dots also within ridge</b> ) seen in <b>acral melanoma</b>
<b>Ulceration</b>	Occurs late in invasive melanoma
<b>BCC</b>	
<b>Blue-gray ovoid nests</b>	Pigmented (blue-gray to brown-gray) ovoid structureless areas seen in pigmented BCC; represents heavily pigmented aggregations of basaloid cells in papillary dermis
<b>Leaf-like areas</b>	Gray-blue leaf-like pattern; represents nests of pigmented BCC cells
<b>Spoke wheel-like structures</b> (Figure 9.3B)	Tan to gray-blue radial projections, no pigment network
<b>Arborizing vessels</b> (Figure 9.3A)	Thickened, discrete branching blood vessels (resemble branches of a tree); represents dilated arterial circulation feeding the tumor (rarely seen in intradermal nevi)
<b>Ulceration</b>	Occurs early in BCCs



**Figure 9.1**

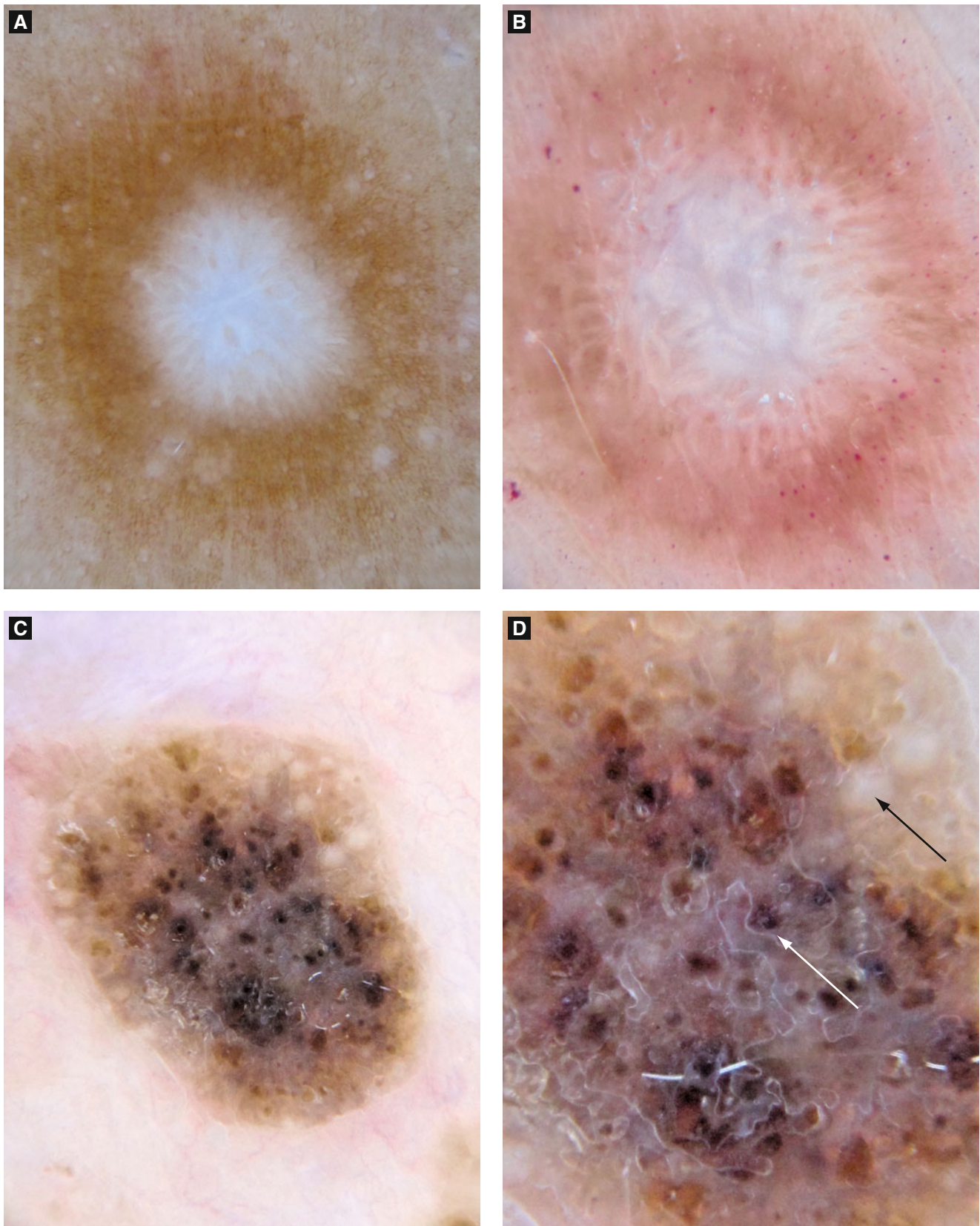
**A: Benign melanocytic nevus (reticular pattern)**

**B: Congenital nevus (globular pattern)**

**C: Benign acral nevus (parallel furrow pattern) (acrosyringia [circle] within ridge, pigment seen in furrow [arrow])**

**D: Blue nevus (homogenous pattern)**

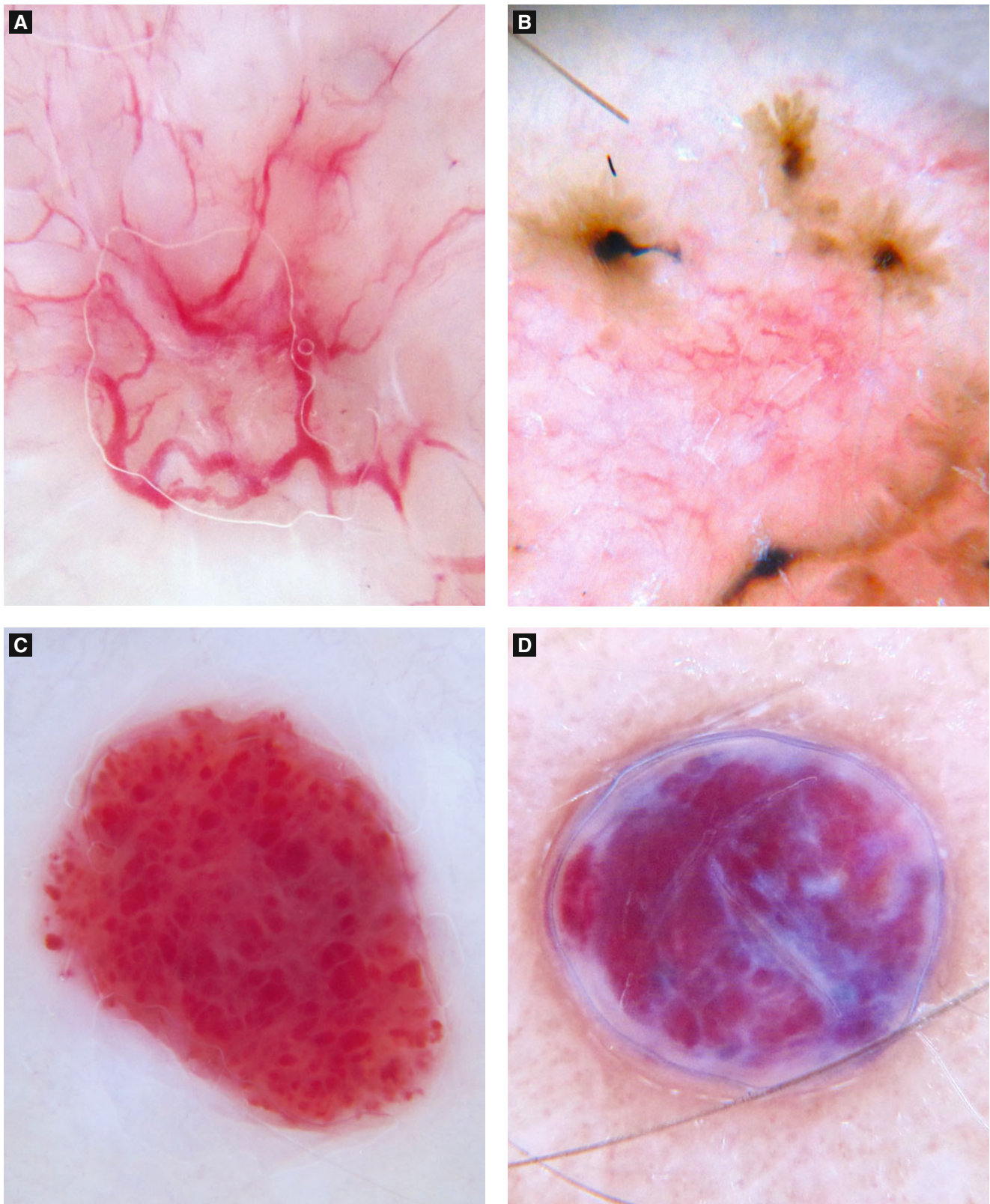




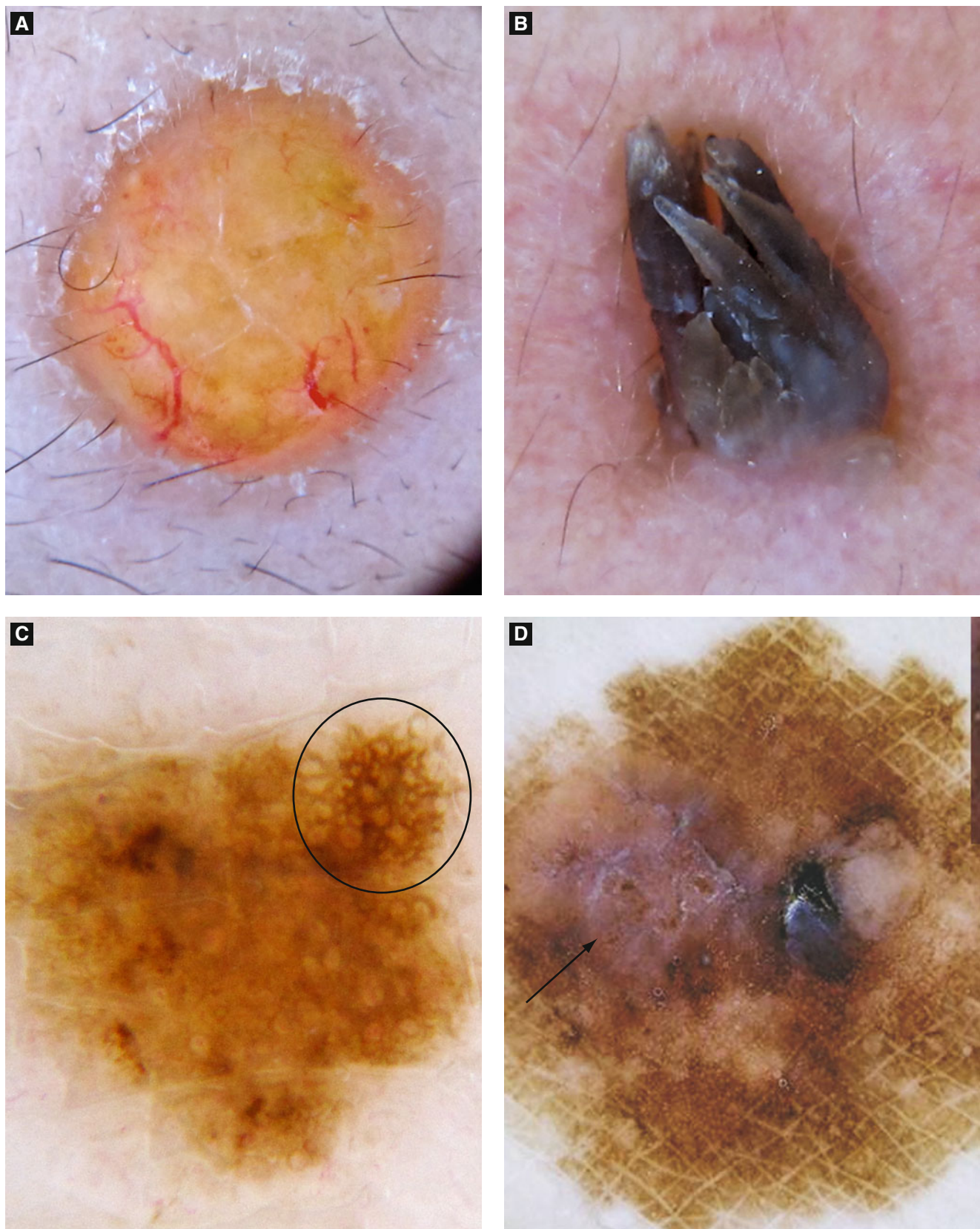
**Figure 9.2**

**A: Dermatofibroma**  
**B: Dermatofibroma**

**C: Seborrheic keratosis (crypts and milia)**  
**D: Seborrheic keratosis, magnified (crypts [white arrow] and milia [black arrow])**

**Figure 9.3****A: BCC (arborizing vessels)****B: BCC (spoke wheel-like structures)****C: Angioma****D: Angioma**





**Figure 9.4**

**A: Xanthogranuloma**

**B: Verruca vulgaris, filiform type**

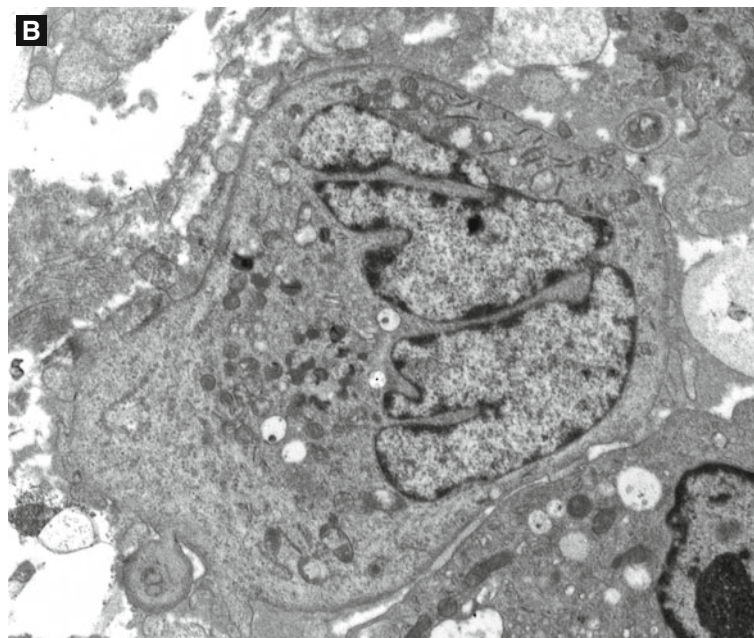
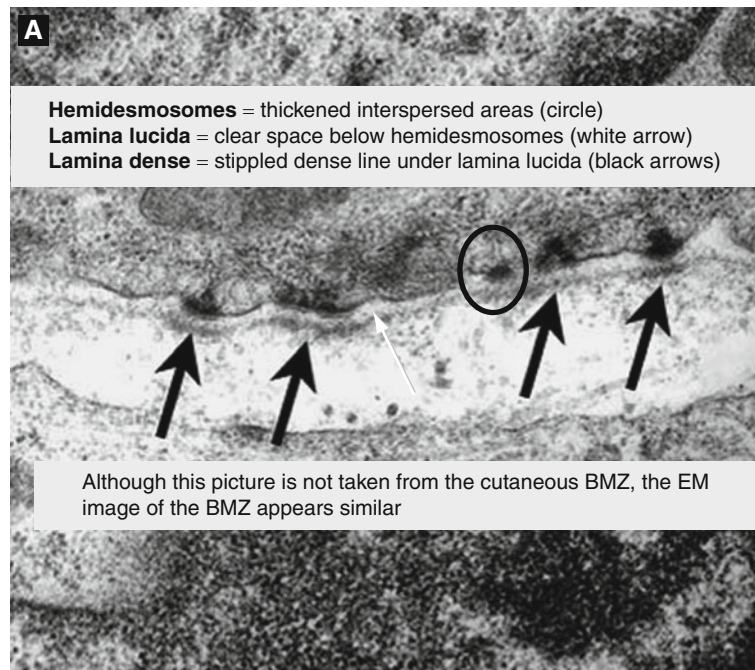
**C: Atypical nevus** (asymmetry with focal irregular reticular network [circle] at periphery with abrupt cutoff)

**D: Melanoma\*** (blue-white veil [seen in papular area and at black arrow], asymmetry, multiple colors)

\* Reprint from Soyer HP, Argenziano G, Hofmann-Wellenhof R, Jorh RH, eds. *Color Atlas of Melanocytic Lesions of the Skin*. New York, NY: Springer; 2007

## 9.2 ELECTRON MICROSCOPY (EM)

- Be able to identify specific images on EM:
  - Dermoepidermal junction (specifically lamina lucida, lamina densa, hemidesmosomes) (Figure 9.5A)
  - Sezary cell (Figure 9.6B)
  - Birbeck granules of Langerhans cell (Figures 9.5B, 9.6A)
  - Others (less often tested): mast cell (Figure 9.6C), Merkel cell, melanocyte with melanosomes

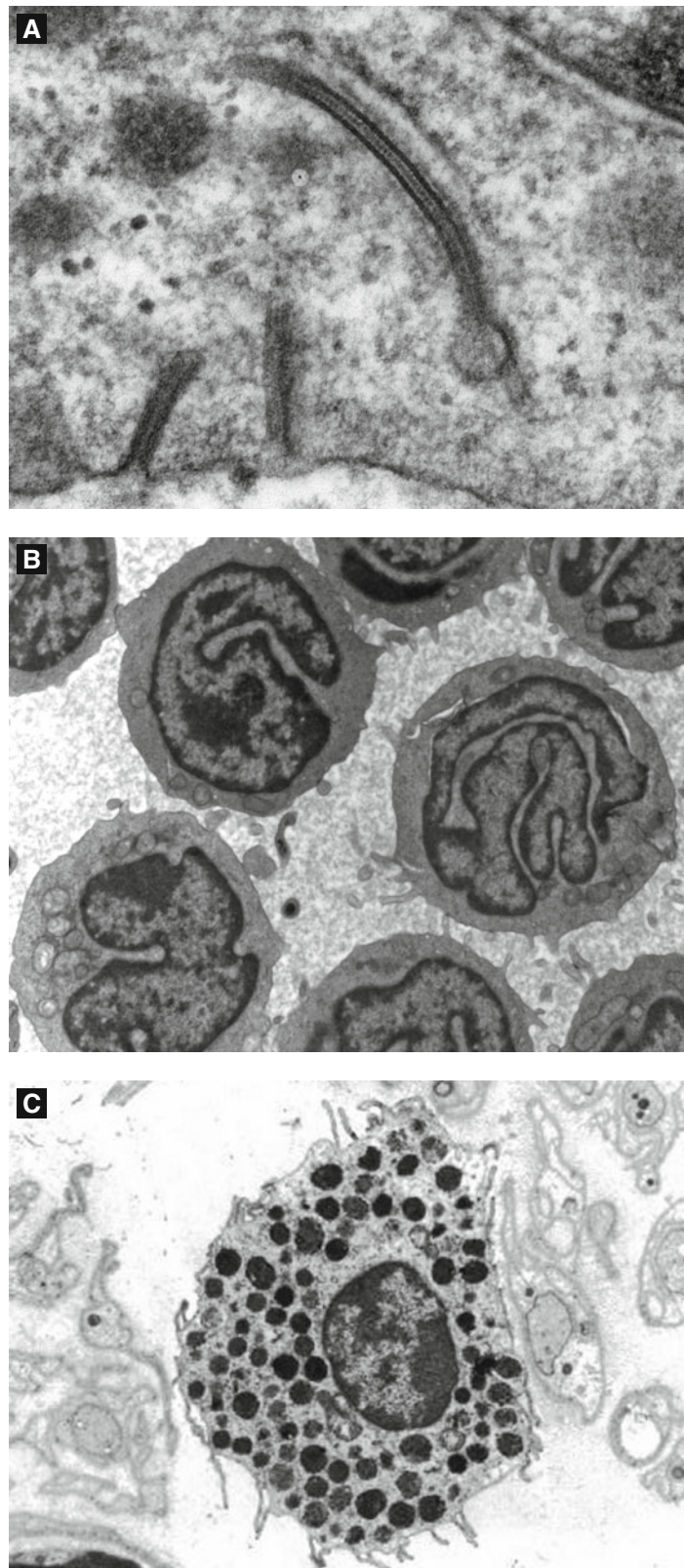


**Figure 9.5**

**A: Basement membrane zone** (Courtesy of Nguyen et al. Lung development in laminin-2 deficiency. *Respir Res.* Feb 2006; 7: 28)

**B: Langerhans cells** (Courtesy of Dr. William L. Clapp, Department of Pathology, University of Florida)





**Figure 9.6**

**A: Birbeck granules (Langerhans cell)\***

**B: Sezary cells\***

*\* Courtesy of Dr. William L. Clapp, Department of Pathology, University of Florida*

**C: Mast cell (from <http://www.medkul.com>, used with permission)**

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# 10

## Life After Boards

### Contents

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10.3 Continuing Medical Education (CME).....	340

## 10.1 TAKING THE JOB

### EMPLOYMENT CONTRACT

- The contract needs to be examined carefully, so it is prudent to hire a contract lawyer before you sign it
- It is best to find a contract lawyer with the following:
  - Experience drafting and negotiating physician employment contracts
  - Experience with contracts specifically in the dermatology field
  - Knowledge of state-specific laws (especially if the contract lawyer is in a different state)
- Important elements in the contract:
  - **Termination Provision**
    - There are two basic types of termination clauses: ‘with cause’ (with good reason) and ‘without cause’
    - ‘Cause’ is typically defined in the contract
    - ‘Without cause’ enables the employer to terminate the contract with no stated reason by providing written notice in advance (often 30 – 180 days)
    - Fair contracts with a ‘without cause’ provision allow the physician employee to do the same
    - In ‘without cause’ terminations, be sure the notice period is long enough to allow for securement of other employment
  - **Restrictive Covenant**
    - Provision that precludes a physician from working in a specific geographic zone (ranging from one to several miles from the practice) for a given time period after the contract terminates
  - **Bonus**
    - If the physician employee’s production exceeds a specific threshold level (which is often 3 to 4 times the base salary), a percentage of collections in excess of the threshold amount goes to the employee as a bonus
  - **Partnership**
    - There may or may not be a track to partnership
    - If partnership track, there is typically a ‘buy in’ amount
  - **Fringe Benefits**
    - Typically includes health insurance, malpractice insurance, disability insurance, CME expenses and time off for CME/vacation, ± retirement plan
  - **Malpractice “Tail”**
    - If the practice’s malpractice policy is maintained on a ‘claims-made’ basis (see below), there should be a provision discussing who is responsible for ‘tail’ coverage of the departing physician (which can be very expensive) if the employment contract terminates
    - There are two types of medical malpractice insurance coverage: occurrence and claims-made
      - Occurrence:
        - Protects a physician from any incident while the policy is in force
        - Does not matter whether the physician is covered when the suit is brought
        - No need to buy ‘tail’ coverage
        - More expensive than claims-made coverage
        - For example, a physician purchases an occurrence policy in 2006, sees patient X in 2007, and terminates the policy in 2008. In 2010, patient X sues the physician for an incident that occurred in 2007. The physician is covered by the occurrence policy (even though the policy has expired) since the incident occurred while the physician had the policy in effect.
      - Claims-made:
        - Protects against a claim as long as the physician is insured when the claim is reported to the insurance company
        - Once the policy is terminated, coverage no longer exists unless ‘tail’ coverage is purchased
        - ‘Tail’ coverage (also called Extended Reporting Period) provides coverage for any claim that is reported after the policy has terminated (incident must have occurred while the physician was insured with an active claims-made policy)
        - For example, a physician purchases a claims-made policy in 2006. The policy is terminated in 2008 but ‘tail’ coverage is purchased. In 2010, patient X sues the physician for an incident that occurred in 2007. The physician is covered because ‘tail’ coverage was purchased.
        - Less expensive than occurrence coverage

## EMPLOYEE VERSUS INDEPENDENT CONTRACTOR

- There are advantages and disadvantages to both, so it is important to understand the differences before making a decision
- **Employee**
  - Financial stability: you do not need to worry about how many patients are canceling per day or if the clinic is slow when starting out since you receive a fixed monthly paycheck
  - Fringe Benefits: health insurance, paid malpractice insurance, ± retirement account, ± health savings account, CME time with stipend
  - Taxes: not complicated since taxes automatically withheld from the paycheck every month
  - Lack of autonomy: biggest disadvantage
- **Independent Contractor (IC)**
  - Autonomy: biggest advantage
  - Tax deduction: any work-related expense (reasonable and customary) can be deducted from taxes as a business expense, such as (but not limited to):
    - Travel: commute to/from work (must be from one office, such as home office, to another office) and other related business travel
    - Licensing and professional association fees, conference dues, journal subscriptions
    - Insurance premium (health care and malpractice insurance)
    - Retirement plan contribution (up to 25% of earnings)
    - Self-employment taxes: FICA tax
- Financial instability:
  - One receives a fixed percentage from the total amount collected (from insurance company/patients) – not the same as the amount billed (which is often much higher)
  - When starting out, it can take several months to build your practice and enlist in different medical insurance plans which means less income early on
- Lack of benefits:
  - You must provide your own health insurance and malpractice insurance; of note, health insurance without a large employer can be quite costly, so weigh this carefully
- Taxes and incorporation:
  - Time and money will be spent to create a corporation, file for an employer identification number (EIN), and to pay an accountant
  - Filing taxes will be much more complicated than if you were an employee

**FICA (Federal Insurance Contributions Act):**  
includes Medicare and Social Security tax

Incorporation: forming of a new corporation (recognized as a legal entity under the law)

## 10.2 CODING AND DOCUMENTATION

Current Procedural Terminology:  
CPT

- Coding can be a frustrating task initially, but it is crucial to learn how to bill properly
- You are ultimately responsible for proper ICD-9 (diagnosis) codes and CPT (procedure) codes regardless of who does the billing in the office; you should also review your own explanation of benefits (EOBs) from the insurance carriers
- If you do not code correctly, claims may be denied or you may be underpaid; thus, it is imperative to understand proper CPT codes, modifiers, and global periods from the start
- ICD9 and CPT codes may be updated, so it is wise to keep up with these changes
- Below is a brief outline for proper coding, which is by no means exhaustive so please refer to additional references for an updated and more detailed explanation
- The best place to read a more detailed explanation is the Centers for Medicare and Medicaid website: [http://www.cms.hhs.gov/MLNEdWebGuide/25\\_EMDOC.asp](http://www.cms.hhs.gov/MLNEdWebGuide/25_EMDOC.asp) (click on Documentation Guidelines for E&M Services on the left hand side)
- Billing form should have the diagnosis listed to the greatest level of specificity

**CODING FOR THE OFFICE VISIT** (Table 10-1)

- The office visit or evaluation/management (E/M) level is determined by documentation of three key components: history, physical exam, and medical decision making
- If counseling accounts for more than 50% of the face-to-face time during the visit, time is considered the controlling factor in determining the level of E/M service (not key components) and the total length of time needs to be documented
- For most visits, E/M level will depend on amount of documentation (not amount counseled)
- **History:**
  - Chief complaint, review of systems (ROS), and personal/family/social history (PFSHx) can be listed as separate elements of the history or included in the description of HPI
  - If a ROS or PFSHx was recorded at an earlier time, it does not need to be re-recorded if there is evidence that the physician reviewed and updated the information (initials/date)
  - Elements (each of the following counts as one element): location, severity, timing, duration, quality, modifying symptoms, context, associated sign/symptoms
- **Physical exam:** need certain number of elements (each bullet in table below = one element)
- **Decision making:** need proper documentation (i.e., follow-up visit, it should be documented in the chart whether the problem is improving, stable, worsening, resolving, etc.)

**Table 10-1 Elements in Physical Exam**  
*(modified to reflect common circumstances in dermatological skin exam)*

System/Body Area	Elements in Physical Exam
Constitutional	<ul style="list-style-type: none"> <li>• General appearance of patient (e.g. <b>well developed, well nourished</b>)</li> <li>• Vital signs, need three or more: BP/P/Temp/Ht/Wt</li> </ul>
Eyes	<ul style="list-style-type: none"> <li>• Inspection of lids and conjunctivae</li> </ul>
Ear/Nose/Throat	<ul style="list-style-type: none"> <li>• Inspection of lips, gum, and teeth</li> <li>• Inspection of oropharynx</li> </ul>
Neck	<ul style="list-style-type: none"> <li>• Examination of thyroid</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>• Examination of peripheral pulses by inspection and palpation</li> </ul>
Lymph nodes	<ul style="list-style-type: none"> <li>• Examination of lymph nodes in neck, axillae, and/or groin</li> </ul>
Extremities	<ul style="list-style-type: none"> <li>• Inspection of digits and nails (clubbing, cyanosis, inflammation, etc.)</li> </ul>
Skin	<ul style="list-style-type: none"> <li>• Palpation of scalp and inspection of hair of scalp, eyebrows, face, chest, extremities, and pubic area (when indicated)</li> <li>• Head (including the face)</li> <li>• Neck</li> <li>• Chest (including breasts and axillae)</li> <li>• Abdomen</li> <li>• Genitalia, groin, buttocks</li> <li>• Back</li> <li>• Each extremity (i.e., RUE and LUE count as two elements)</li> <li>• Inspection of eccrine and apocrine glands of skin and subcutaneous tissue</li> </ul>
Neurologic/Psychiatric	<ul style="list-style-type: none"> <li>• Orientation to time, place, and person</li> <li>• Mood and affect (e.g., depressed, anxious, agitated, <b>pleasant</b>)</li> </ul>



**NEW OUTPATIENT E/M CODES (Table 10-2)****99201 – Focused visit**

- Problem focused history (established chief complaint and 1–3 HPI elements)
- Problem focused exam (1–5 elements)
- Straightforward medical decision making (self-limited or minor problem)
- Time spent: 10 min

Need all 3 key components for new visit

**99202 – Expanded visit**

- Expanded problem focused history (1–3 HPI elements), no ROS or PFSHx required
- Expanded problem focused exam (6–11 elements)
- Straightforward medical decision making
- Time spent: 20 min

**99203 – Detailed visit**

- Detailed history
  - Establish chief complaint, ≥4 HPI elements in HPI or status of 3 chronic conditions
  - Extended problem pertinent ROS (includes 2–9 systems)
  - Patient's past history, family history, OR social history (1 PFSHx)
- Detailed exam (≥12 elements)
- Low complexity (one new problem) medical decision making
- Time spent: 30 min

**99204 – Comprehensive visit**

- Comprehensive history: ≥4 HPI elements or status of 3 chronic conditions, complete ROS (≥10 systems), one element each from PHx, FHx, and SHX (3 PFSHx)
- Comprehensive exam: complete single system specialty or complete multisystem exam
- Moderate complexity decision making
- Time spent: 45 min

**99205 – Comprehensive visit**

- Comprehensive history/exam, high complexity decision making; time spent: 60 min

**ESTABLISHED OUTPATIENT E/M CODES (Table 10-3)****99211 – Focused visit (nurse visit)**

- Key components not required; physician need not be present (only supervising)
- Minimal evaluation/management (E/M); time spent: 5 min

Need 2 out of 3 components for established visit

**99212 – Problem focused visit**

- Problem focused history (chief complaint and 1–3 HPI elements)
- Problem focused physical exam (1–5 elements)
- Straightforward or self-limited medical decision making
- Time spent: 10 min

**99213 – Expanded problem visit**

- Expanded problem focused history (1–3 HPI elements, 1 ROS)
- Expanded problem focused physical exam (≥6 elements)
- Low complexity decision making (one new problem or one worsening problem or two stable problems)
- Time spent: 15 min

Expanded HPI with low complexity decision making will be 99213 regardless of physical exam elements

**99214 – Detailed visit**

- Detailed history (≥4 HPI elements or status of 3 chronic conditions, 2–9 ROS, 1 PFSHx)
- Detailed exam (≥12 elements)

**Table 10-2 New Outpatient E/M Codes**

Key Components (Need All 3)	99202	99203	99204	99205
History	<b>Expanded</b> (1–3 HPI elements, 1 ROS)	<b>Detailed</b> (≥4 elements, 2–9 ROS, 1 PFSHx)	<b>Comprehensive</b> (≥4 elements, 10 ROS, 3 PFSHx)	<b>Comprehensive</b> (≥4 elements, 10 ROS, 3 PFSHx)
Physical exam	<b>Expanded</b> (6–11 elements)	<b>Detailed</b> (≥12 elements)	<b>Comprehensive</b> (≥12 elements)	<b>Comprehensive</b> (≥12 elements)
Medical decision making	<b>Straightforward</b>	<b>Low complexity</b> (1 new, 2 stable, or 1 worsening)	<b>Moderate complexity</b>	<b>High complexity</b>
Time spent	<b>20 min</b>	<b>30 min</b>	<b>45 min</b>	<b>60 min</b>

**Table 10-3 Established Outpatient E/M Codes**

Key Components (Need 2 of 3)	99212	99213	99214	99215
History	<b>Problem focused</b> (1–3 HPI elements)	<b>Expanded</b> (1–3 elements, 1 ROS)	<b>Detailed</b> (≥4 elements, 2–9 ROS, 1 PFSHx)	<b>Comprehensive</b> (≥4 elements, 10 ROS, 3 PFSHx)
Physical exam	<b>Problem focused</b> (1–5 elements)	<b>Expanded</b> (6–11 elements)	<b>Detailed</b> (≥12 elements)	<b>Comprehensive</b> (≥12 elements)
Medical decision making	<b>Straightforward</b>	<b>Low complexity</b> (1 new, 2 stable, 1 worse)	<b>Moderate to high complexity</b>	<b>High complexity</b>
Time spent	<b>5 min</b>	<b>10 min</b>	<b>25 min</b>	<b>40 min</b>

- Moderate to high complexity medical decision making
- Time spent: 25 min

**99215 – Comprehensive visit**

- Comprehensive history (≥4 HPI elements or status 3 conditions, ≥10 ROS, 3 PFSHx)
- Comprehensive exam: complete single system specialty or complete multisystem exam
- High complexity medical decision making
- Time spent: 40 min

**Important Points**

- The limiting factor for determining the level of a new office visit depends on the physical exam, since 12 elements are needed
- Most new office visits will be 99202 unless you do a thorough physical exam (12 elements)
- If you were to do just do a waist up exam, you could code 99203 if you examined the following (the number of elements for each bold term is in parenthesis):  
 General: **Pleasant, WDN, alert/oriented** female in no distress (3 elements)  
**Face, neck, chest, back, abdomen, LUE, RUE, eyes, oral mucosa** (9 elements)

**CODING FOR PROCEDURES****Global Period**

- A global period for a procedure is the duration of time included for non-billable routine surgical follow-up after the affiliated procedure
- Routine care such as suture removal, dressing changes, and follow-up during the postoperative period cannot be billed if it falls within the global period
- If the visit is unrelated to the procedure or if there is an unexpected complication from the surgery (i.e., hematoma), then you will get reimbursed as long as you code it properly

Procedures with NO GLOBAL PERIOD		
<b>• Biopsies:</b>		<b>• Others:</b>
⇒ Skin biopsy (11100)	⇒ IL injections (11900–11901)	
⇒ Skin biopsy add-on (11101)	⇒ Shave removals (11300–11313)	
⇒ Eyelid biopsy (67810)	⇒ Paring/cutting benign hyperkeratotic lesions (11055–11057)	
⇒ External ear biopsy (69100)	<b>• Mohs micrographic surgery:</b>	
⇒ Lip biopsy (40490)	⇒ Head, neck, hands, feet, genitalia (17311, 17312)	
⇒ Vulvar biopsy (56605)	⇒ Trunk, arms, legs (17313, 17314, 17315)	
⇒ Penile biopsy (54100)		
⇒ Nail biopsy (11755)		
Excision Codes – 10 DAY GLOBAL PERIOD		
<b>• Benign Excision</b>		<b>• Malignant Excision</b>
⇒ Trunk, arms, legs (11400–11406)	⇒ Trunk, arms, legs (11600–11606)	
⇒ Scalp, neck, hands, feet, genitalia (11420–11426)	⇒ Scalp, neck, hands (11620–11626)	
⇒ Face, eyelids, ears, nose, lips (11440–11446)	⇒ Face, eyelids, ears, nose, lips (11640–11646)	
Destruction Codes – 10 DAY GLOBAL PERIOD		
<b>• Premalignant</b>		<b>• Destruction of lesion in genital area</b>
⇒ First lesion (17000)	⇒ Anal, simple chemical (46900)	
⇒ Additional lesions, up to 14 (17003)	⇒ Anal, electrodesiccation (46910)	
⇒ ≥15 lesions (17004)	⇒ Anal, cryosurgery (46916)	
<b>• Benign</b>	⇒ Anal, laser surgery (46917)	
⇒ 1–14 lesions (17110), ≥15 lesions (17111)	⇒ Anal, surgical excision (46922)	
<b>• Malignant</b>	⇒ Penile, simple chemical (54050)	
⇒ Trunk, arms, legs (17260–17266)	⇒ Penile, electrodesiccation (54055)	
⇒ Scalp, neck, hands, feet, genitalia (17270–17276)	⇒ Penile, cryosurgery (54056)	
⇒ Face, eyelids, ears, nose, lips (17280–17286)	⇒ Vulva, any method (56501)	
	⇒ Vulva, extensive (56515)	
Repairs – 10 DAY GLOBAL PERIOD		
<b>• Simple Repair</b>	<b>• Intermediate Repair</b>	<b>• Complex Repair</b>
⇒ Scalp, neck, trunk, extremities, hands, feet (12001–12007)	⇒ Scalp, trunk, extremities (12031–12034)	⇒ Trunk (13100–13102)
⇒ Face, ears, lips, mucous membranes (12013–12018)	⇒ Neck, hands, feet (12041–12044)	⇒ Scalp, arms, legs (13120–13122)
	⇒ Face, ears, eyelids, nose, lips (12051–12053)	⇒ Face, neck, hands, feet (13131–13133)
		⇒ Eyelids, nose, ears, lips (13150–13153)
Flaps and Grafts – 90 DAY GLOBAL PERIOD		
<b>• Adjacent Tissue Transfer/Rearrangement</b>		<b>• Others</b>
⇒ Trunk (14000–14001)	⇒ Skin substitute or replacement such as graft (15000–15431)	
⇒ Scalp, arms, legs (14020–14021)		
⇒ Forehead, cheeks, chin, mouth, H/F (14040–14041)		
⇒ Eyelids, nose, ears, lips (14060–14061)		
⇒ ≥30 cm <sup>2</sup> area – unusual or complicated (14300)		

**Modifiers (Table 10-4)**

- A modifier is a two digit code appended to a CPT code to indicate a special circumstance when reporting a service
- Many procedure codes are bundled together and if those bundled code combinations are billed together, generally Medicare will only reimburse one of the codes, typically the one with the lower value
- Many insurance companies follow the bundling edits of Medicare, so it is important to know which codes are bundled together
- The use of modifiers helps to communicate with computer programs to override these bundling edits in the software programs
- Modifiers are also critical during the global period in ensuring that providers receive reimbursement for services unrelated to the primary procedures, in addition to staged procedures, multiple procedures, and evaluation and management (E&M) services
- Correct Coding Initiative (CCI) is Medicare's national editing software system that bundles various procedural code combinations
- A CCI edit is a pair of CPT codes that are not separately payable except under certain circumstances, and it requires careful monitoring because these edits are updated quarterly by Centers for Medicare and Medicaid (CMS)
- CCI edits apply to all physicians who bill for services on the Medicare claims processing form, and the edits may be obtained via the CCI Edits Manual by going to the CMS website (<http://www.cms.hhs.gov/NationalCorrectCodInitEd/>), where a listing of the CCI edits by specific CPT sections is available for free downloading

Not bundled	Bundled
<ul style="list-style-type: none"> <li>• Skin biopsy (11100) + site-specific skin biopsy (lip, external ear, genitalia, etc.)</li> <li>• Destruction of AKs + destruction of malignant lesion</li> </ul>	<ul style="list-style-type: none"> <li>• Destruction of AKs (17000) + skin biopsy (1110)</li> <li>• Destruction of AKs (17000) + excision of malignant lesion</li> <li>• Excision of malignant lesion + adjacent tissue transfer</li> </ul> <p>Adjacent tissue transfer code has excision already included, so cannot bill separately for excision</p> <ul style="list-style-type: none"> <li>• MOHS procedure + pathology (path is integral part of MOHS reimbursement, so cannot be billed separately)</li> <li>• Office visit + procedure</li> <li>• Two procedures on same visit (i.e., biopsy and excision)</li> <li>• Two procedures with exact same CPT code</li> </ul>

**Table 10-4 Common Modifiers**

Modifier	Description	Comments
<b>24</b>	Unrelated E/M service by same physician during postoperative period of procedure	Shows E/M unrelated to the surgery; modifier only attached to E/M visits (99XXX), not procedure codes
<b>25</b>	Significant and separately identifiable E/M service by same physician on same day of procedure or other service	<ul style="list-style-type: none"> <li>• Attach this modifier only to codes related to E/M visits (99xxx), not procedure codes</li> <li>• Must have substantial documentation that satisfies criteria for respective E/M level</li> </ul>
<b>58</b>	Re-excision during postoperative period by same physician	• Use for planned staged excision, re-excision of incompletely excised lesion, or wider excision to obtain further margins after initial excision (i.e., wider excision for melanoma)
<b>59</b>	Distinct and independent procedure performed on the same day as another procedure	• Used to report services that are not normally reported together but are appropriate under the circumstance (used to unbundle same day surgical services); attach modifier to procedure code
<b>79</b>	Unrelated procedure or service by same physician during the postoperative global period of a procedure	<ul style="list-style-type: none"> <li>• Indicates the performance of a procedure during a postoperative period which was unrelated to the postoperative care of the original procedure</li> <li>• Always put this modifier first (i.e., 17110–79, 59)</li> </ul>
<b>91</b>	Repeat clinical diagnostic lab test	• If two KOHs or scabies preps performed at two different sites, use this modifier



- CCI versions are updated quarterly (January, April, July, and October)
- When looking at the CCI table, there will be either a 0 or 1 next to the CPT code, which is the indicator code for the associated CPT code relaying if a particular modifier will indeed override the computer edit and result in reimbursement; zero indicates no circumstances in which modifier appropriate, and the number one indicates modifier is allowed to distinguish between services provided (i.e., modifier 59 will override the computer “edit” and thus result in reimbursement)
- The examples below are to show there is no rhyme or reason as to which codes are bundled
- **CCI edits must be used that were in effect that quarter so the edits below will likely have already changed**

### Important Points

- The postoperative day does not start until the day after the procedure
- Use modifier 79 for complications during the postoperative period (i.e., hematoma)
- If performing an excision on one day and the repair is on another day, both can be reimbursed with modifier 58 (need medically necessary reason for delaying the repair)
- Cannot bill a biopsy code with another surgical service for the same EXACT lesion on the same day (i.e., for clinical BCC, cannot bill for biopsy and C&D)
- If you are covering for another physician in your group, cannot bill for a suture removal or dressing change visit if related to the original procedure and still within the global period
- Multiple reduction rule in surgery: first procedure paid at 100%, but second and any additional is paid at 50%
- When lesion excised and requires only simple closure, cannot bill for simple repair (12001–12018) since this is considered part of the reimbursement for the excision
- When medical records are requested by an insurance company, be sure to review every document before sending it; if you need to make any addendums, use the current date and time (do not back date)

Following applies to Medicare and many other insurance carriers

### Coding Examples

- Removal of a 0.7×0.7 cm atypical nevus (on arm) with 2 mm margins on either side via mid-dermal shave technique → 11301 (shave removal for 0.6–1.0 cm lesion) or 11100 (biopsy code if unsure whether removed completely); unable to bill for excision (11401) since it is not a full thickness removal through the dermis; unable to bill 11302 (1.1–2.0 cm) since uninvolved margins are not added to diameter of a shave removal
- Removal of 0.5×0.5 cm atypical nevus (arm) with 6 mm circular blade (punch excision) with one superficial suture → 11401 (excision 0.6–1.0 cm); able to bill for excision since it is a full thickness removal; lateral margins are added to determine excised diameter in excisions (unlike shave removals)
- Atypical nevus removed and pathology report consistent with moderate to severe cytologic atypia with recommendation for wider clinical excision → ICD9 code 238.2; would not be coded as a malignant diagnosis or malignant excision code
- Removal of a 0.7×0.4 cm atypical nevus (chest) performed with 2 mm margins on either side in elliptical excision → 11402 (excision, trunk 1.1–2.0 cm); use lesion’s widest diameter (0.7 cm) plus margins (0.2+0.2) to determine proper excised diameter (1.1 cm)
- Malignant growth excised but unable to do primary closure so transposition flap constructed and used to close site → 14000 only; unable to bill excision (benign or malignant) code as flap code includes the excision and should not be reported separately
- Patient was seen last week for treatment of actinic keratoses and now comes back 8 days later for a new problem (i.e., new growth) and you perform a biopsy → 99213 (modifier 24, 25), 11100 (modifier 79); must use postop modifiers as you are still in 10 day global period
- Patient was seen last week for a growth on the hand and you performed a biopsy and now 8 days later patient comes in for new problem (actinic keratoses) which you treat with liquid nitrogen → 99213 (modifier 25), 17000, 17003 (no modifier); no postop modifiers needed in this case as a biopsy has no global period
- Patient seen 11 days after cryodestruction of actinic keratoses for a site which was treated (i.e., painful or infected) → 99213 (no modifier); no modifier needed since after 10 day global period of premalignant cryodestruction

### DOCUMENTATION

- Proper documentation is important for several reasons:
  - There is an ethical and professional obligation (failure to do so may lead to loss of hospital privileges and even, in extreme cases, one’s medical license)
  - Allows support for billing at the appropriate level of service

- Poor documentation can result in lost income as Medicare and other insurers are paying more attention to documentation with random audits
- May help in the event of a potential malpractice claim (poor documentation will absolutely hurt the case); quality of documentation can determine a defensible malpractice case versus an indefensible one
- Best to document as if a Medicare claims examiner (or better yet, a plaintiff's attorney) were reading the medical record over your shoulder
- Basic mnemonic for good documentation: LAWSUIT (legible, accurate, whole or complete, substantiated, unaltered, intelligible, timely)
- Important points in the medical record
  - Do not leave blank areas in chart – if any blank areas, cross out so they cannot be used for out-of sequence entries
  - If patient is noncompliant with medication instruction or advice, this should be documented (add verbatim quote from patient in quotation marks if appropriate)
  - Document no-show or missed appointments and follow-up efforts to reschedule visits
  - Always ask and document pertinent medical history (as this is a common factor in malpractice claims); case law reflects that it is not the patient's responsibility to volunteer information, but the physician's duty to ask appropriate questions
- If the medical record is copied, there should ideally be a dated recording of this

### 10.3 CONTINUING MEDICAL EDUCATION (CME)

- All physicians are required to participate in continuing medical education (CME), and each state licensing board mandates a minimum number CME credits for licensure renewal
- The required number of CME credits varies from state to state, and it must be completed within the license cycle (which typically is either two or three years)
- Also, certain states may have specific requirements for CME credits in particular areas, such as patient safety or risk management
- The most accepted type of CME credit is the American Medical Association (AMA) Physician's Recognition Award (PRA) Category 1 Credit
- In order to help physicians identify accredited CME providers, the AMA requires its providers to trademark the credit phrase: AMA PRA Category 1 Credit™
- Two types of AMA PRA credits: category 1 credit (formal activities) and category 2 credit (non-supervised activities)
- **AMA PRA Category 1 Credit™**
  - Provider designated activities: accredited CME provider issues credit to physician after completing CME activity such as:
    - Live activities (conferences, workshops, seminars, etc.)
    - Journal-based CME
    - Enduring material (educational activity in print, online, video, etc.)
    - Internet point of care learning (self-directed online learning)
  - Direct credit activities: physician directly receives AMA PRA Category 1 Credit™ from AMA after filling out Direct Credit Application (found on AMA website) with appropriate documentation and processing fee (typically around \$75 for non-AMA members, approximately \$30 for AMA members), includes following:
    - Teaching in live CME activity
    - Publishing an article (up to 10 credits if lead author) or presenting poster (5 credits)
    - Board certification exam completion (25 credits of AMA PRA Category 1 Credit™)
    - Independent learning
- **AMA PRA Category 2 Credit**
  - Non-supervised activities; completely self-claimed and self-documented by the physician; physician determines number of credits received based on time spent (60 min equivalent to 1 credit); activities should be documented ideally with date, title, content, hours spent in activity with appropriate number of designated credits; includes following:
    - Teaching medical students and/or residents
    - Online learning
    - Reading medical literature, medical writing, and research

- Small group discussions
- Preceptorship
- Live activities not designated for AMA PRA Category 1 Credit™
- AMA PRA Category 1 Credit™ is recognized and accepted across all jurisdictions and medical organizations/boards
- Typically there is a minimum number of category 1 credits required and a maximum number of category 2 credits allowed for licensure renewal
- Due to minimum AMA PRA Category 1 Credit™ requirement, it is important to identify legitimate AMA PRA Category 1 activities
- There are non-accredited organizations that will advertise “Category 1 Credits™” or “CME’s offered,” but it is important to be aware these are not equivalent to AMA PRA Category 1 Credits™
- There is no central database for physicians to track number of CME credits
- It is important to log all of the CME activities with the certificates of completion because the state licensing board can perform a random audit, in which case you must show evidence of completion of the required hours
- The duration of time to hold on to CME credit certificates will depend on how long the specific medical licensing board requires a CME history (typically between 2 and 6 years)

## References

1. AMA website, section on CME: <http://www.ama-assn.org/ama/pub/education-careers/continuing-medical-education/frequently-asked-questions.shtml>.
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# 11

## High Yield Facts and Buzz Words

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## 11.1 GENETIC DISEASES

Disease	Inh	Gene Mutation	Clinical Findings
<b>Acrodermatitis Enteropathica</b>	AR	SLC39A4	Scaly eczematous plaques over the perioral, perineal, and acral areas (hands/feet)
<b>AEC Syndrome</b> (Hay-Wells Syndrome)	AD	P63 (p63 protein)	Erosive scalp dermatitis, 80% cleft lip/palate, ankyloblepharon, hypotrichosis
<b>Albinism, Oculocutaneous Type 1</b>	AR	TYR (tyrosinase)	Severe nystagmus, ↑ SCC risk, pink nevi
<b>Albinism, Oculocutaneous Type 2</b>	AR	P (P protein)	Nystagmus, light brown hair, pigmented nevi
<b>Albinism, Oculocutaneous Type 3</b>	AR	TRP-1 (tyrosine-related protein)	Nystagmus, blue/brown iris, light brown hair/skin
<b>Albright Hereditary Osteodystrophy</b>	AD	GNAS1 (encodes $\alpha$ subunit for stimulatory G protein of adenylate cyclase: Gs)	Pseudohypoparathyroidism, short stature, shortened fourth metacarpal, soft tissue calcification and ossification (i.e., osteoma cutis)
<b>Alkaptonuria</b>	AR	HGD (homogentisate oxidase)	Dark urine on standing, ochronosis, valvular heart disease, arthritis, renal calculi, red-black ear wax
<b>Ataxia-Telangiectasia</b> (Louis-Bar Syndrome)	AR	ATM (ataxia-telangiectasia mutated: chromosomal strand break repair)	↑ Leukemia/lymphoma, ↑ sensitivity to ionizing radiation, ↑ sinopulmonary infections, progressive ataxia, telangiectasias
<b>Atrichia with Papules</b> (Congenital Atrichia with Papules)	AR	HR (hairless gene: zinc finger)	Normal hair at birth but not replaced after hair sheds, follicular papules ( $\pm$ resembles keratosis pilaris)
<b>Bannayan–Riley–Ruvalcaba Syndrome</b>	AD	PTEN (tumor suppressor gene)	Macrocephaly, lipomas, hemangiomas, genital lentigines, trichilemmomas, ↑ breast/thyroid/GI cancer (CA)
<b>Bazex Syndrome</b> (Bazex-Dupre-Christol)	XLD	Unknown (gene linked to Xq24–q27)	Multiple BCCs, hypotrichosis, hypohidrosis, follicular atrophoderma (circumscribed areas on dorsal hands/feet)
<b>Beare-Stevenson Cutis Gyrata Syndrome</b>	AD	FGFR2 (fibroblast growth factor receptor 2)	Cutis gyrata, acanthosis nigricans, craniosynostosis (premature fusion of certain bones in skull)
<b>Beckwith–Wiedemann Syndrome</b>	AD (<15%)	CDKN1C (cyclin-dependent kinase inhibitor 1c, aka p57, or Kip2)	Macroglossia, circular depression (helices of ears), gigantism, midline abdominal wall defects, neonatal hypoglycemia, organomegaly, ↑ Wilms tumor
<b>Berardinelli-Seip Syndrome</b> (Congenital Generalized Lipodystrophy)	AR	BSCL2	Acanthosis nigricans, type 2 diabetes mellitus, generalized lipodystrophy
<b>Birt–Hogg–Dubé Syndrome</b>	AD	FLCN (folliculin)	↑ Fibrofolliculomas, trichodiscomas, lipomas, ↑ CA (renal/colon/medullary thyroid), lung cysts
<b>Björnstad Syndrome</b>	AR, AD	BCS1L	Deafness, pili torti
<b>Bloom Syndrome</b>	AR	BLM (RECQL3: DNA helicase)	Oral SCC, leukemia/lymphoma, GI CA, ↑ infections, poikiloderma, photosensitivity, hypogonadism
<b>Brooke–Spiegler Syndrome</b>	AD	CYLD (cylindromatosis)	Multiple trichoepitheliomas, cylindromas, spiradenomas, $\pm$ BCCs

Continued on the next page

Disease	Inh	Gene Mutation	Clinical Findings
<b>Bruton Agammaglobulinemia</b>	XLR	BTK (Bruton tyrosine kinase)	↓ B cells with ↓ Ig levels, eczema resembling atopic dermatitis, recurrent bacterial infections like impetigo/furunculosis (especially from encapsulated organisms)
<b>Buschke–Ollendorf Syndrome</b>	AD	LEMD3	Osteopoikilosis, connective tissue nevi (dermatofibrosis lenticularis disseminata)
<b>Carney Complex</b> (LAMB Syndrome) (NAME Syndrome)	AD	PRKAR1α (protein kinase c-AMP-dependent regulatory type 1 α)	Psammomatous schwannomas, thyroid disease, multiple lentigines, blue nevi, testicular tumors, cutaneous and cardiac myxomas
<b>Chédiak–Higashi Syndrome</b>	AR	LYST1 (lysosomal transport)	Oculocutaneous albinism, ataxia, giant lysosomal granules, muscle weakness
<b>CHILD syndrome</b> (Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects)	XLD	EBP gene (emopamil binding protein)	Unilateral ichthyosiform erythroderma, limb/visceral hypoplasia, stippled epiphyses
<b>Chondrodysplasia Punctata</b>	XLR	Arylsulfatase E	Ichthyosis, sparse hair, stippled epiphyses (punctate chondral calcifications)
<b>Chondrodysplasia Punctata, Rhizomelic</b>	AR	PEX7 (peroxisomal biogenesis disorder)	Stippled epiphyses, accumulation of phytanic acid, follicular atrophoderma, scarring alopecia, cataracts, rhizomelia (striking shortening of proximal limbs)
<b>Chondrodysplasia Punctate, XLD</b> (Conradi–Hünemann–Happle Syndrome)	XLD	EBP (emopamil-binding protein)	Ichthyosiform erythroderma (along lines of Blaschko), follicular atrophoderma, patchy alopecia, cataracts, stippled epiphyses
<b>Chronic Granulomatous Disease</b>	XLR (mostly)	CYBB (cytochrome B, b subunit → phagocyte NADPH oxidase defect, so unable to deliver respiratory burst for catalase-positive bacteria)	Recurrent infections, initially with staph infections around ears/nose, lymphadenopathy, cutaneous abscesses, suppurative lymphadenitis
<b>Citrullinemia</b>	AD	ASS (argininosuccinate synthetase, in urea cycle)	Lethargy, poor feeding, seizures, vomiting
<b>Cockayne Syndrome</b>	AR	ERCC8 (CSA) ERCC6 (CSB)	Premature aging, cataracts, cachectic dwarfism, retinitis pigmentosa, photosensitivity
<b>Congenital Contractural Arachnodactyly</b>	AD	FBN2 (fibrillin-2)	Crumpled ears, arachnodactyly, long limbs, scoliosis
<b>Congenital Ichthyosiform Erythroderma</b> (Nonbullous CIE)	AR	TGM1 (transglutaminase-1) ALOX12B (lipoxygenase) ALOXE3 (lipoxygenase)	Collodion membrane, generalized erythroderma with fine scaling (flexural involvement), palmoplantar keratoderma (PPK)
<b>Cowden Syndrome</b> (Multiple Hamartoma Syndrome)	AD	PTEN (tumor suppressor gene)	Trichilemmomas, oral papillomas, ↑ CA (breast, thyroid follicular, colon), fibrocystic breast changes, cobblestoning of mucosa
<b>Cutis Laxa</b>	AR	FBLN5 (fibulin 5)	Loose pendulous skin with decreased elasticity, diverticulae (bladder/GI), pulmonary emphysema, pulmonary artery stenosis
<b>Cutis Laxa</b>	AD	ELN (elastin), FBLN5	Loose pendulous skin, systemic involvement uncommon

Continued on the next page

Disease	Inh	Gene Mutation	Clinical Findings
<b>Cutis Laxa</b> (Occipital Horn Syndrome, EDS IX)	XLR	ATP7A (copper transport disease)	Mild skin laxity, skeletal malformations, GU tract abnormalities, joint laxity
<b>Darier Disease</b> (Darier–White Disease) (Keratosis Follicularis)	AD	SERCA2 (calcium-dependent ATPase 2A2)	Acrokeratosis verruciformis, warty papules/plaques in seborrheic distribution, red/white longitudinal streaking of nails with v-shaped nicks at free margin
<b>Dyskeratosis Congenita</b> (Zinsser-Engman-Cole Syndrome)	XLR	DKC1 (dyskerin: ribosome assembly chaperone)	Reticulate gray brown hyperpigmentation, dystrophic nails, alopecia, premalignant leukoplakia, pancytopenia, continuous lacrimation, ↑ malignancy
	AD	TERC (telomerase RNA component)	
<b>EB Recessive Dystrophic</b> (RDEB-HS) (Hallopeau-Siemens) Split at sublamina densa	AR	Type VII collagen ( <b>premature termination codon</b> )	Severe widespread bullae at birth, scarring on hands/feet (mitten deformity), nail dystrophy, mucosal strictures, ↑ oral/esophageal/skin SCCs
<b>EB, Dominant Dystrophic</b> (DDEB) (Cockayne-Touraine)	AD	Type VII collagen (anchoring fibrils)	Bullae mainly over extremities, nail dystrophy, less severe than RDEB
<b>EB Simplex</b> (Dowling-Meara) Split at basal layer	AD	K5/14 (EM: <b>clumped tonofilaments</b> in basal layer)	Herpetiform bullae, early death, PPK, nail dystrophy, mucosal involvement (laryngeal, esophageal)
<b>EB Simplex</b> (EBS) (Weber-Cockayne) (Localized)	AD	K5/14 (keratin)	Onset in childhood, bullae mainly in extremities (hands, feet), heals without scarring
<b>EBS with Muscular Dystrophy</b>	AR	Plectin (hemidesmosome)	Muscular (myotonic) dystrophy, widespread bullae at birth, scarring, early death
<b>EB Junctional</b> (JEB) (Herlitz) (EB Lethalis) Split at lamina lucida	AR	LAMA3 (subunit of <b>laminin 5</b> , now called <b>laminin 332</b> ) ( <b>premature termination codon</b> )	Widespread bullae, exuberant perioral granulation tissue, early death, enamel defects, severe mucosal involvement (respiratory/GI tract), ± hoarseness
<b>EB Junctional</b> (Non-Herlitz) (Generalized Atrophic Benign EB)	AR	Laminin 332 (5) or BPAG2	Bullae, mild oral involvement, scarring alopecia, improves over time
<b>EB Junctional with Pyloric Atresia</b>	AR	$\alpha 6\beta 4$ (integrin)	Bullae, pyloric atresia, hydronephrosis, mucosal erosions
<b>Ectodermal Dysplasia with Skin Fragility</b>	AD	Plakophilin 1 and 2 (mainly)	Fragile bullae and erosions/crust, perioral fissuring and cheilitis, PPK, nail dystrophy
<b>EEC Syndrome</b> (Ectrodactyly, Ectodermal Dysplasia, Cleft Lip/Palate)	AD	p63 gene	Cleft lip/palate, ectodermal dysplasia, ectrodactyly (absence of one or more central digits of hand or foot, also called ‘lobster claw deformity’)
<b>Epidermodysplasia Verruciformis</b>	AR	EVER1, EVER2	Abnormal susceptibility to human papillomaviruses of the skin (often HPV 5/8/47), ↑ SCCs
<b>Epidermolytic Hyperkeratosis</b> (Generalized EHK) (Bullous CIE)	AD	K1, K10 (clumping of keratin filaments in suprabasal layers)	Erythema/blistering in infancy and replaced by hyperkeratosis (flexural predominance)
<b>Erythrokeratoderma Variabilis</b> (Mendes da Costa)	AD (mainly)	GJB3 and GJB4 (connexin 31 and 30.3)	Transient erythematous figurate patches, fixed hyperkeratotic plaques
<b>Fabry Disease</b> (Angiokeratoma Corporis Diffusum)	XLR	$\alpha$ -Galactosidase A	Angiokeratomas, pain/paresthesia of limbs, whorled corneal opacities, hypohidrosis, renal and coronary insufficiency, “maltese crosses” (birefringent lipids in urine)

Continued on the next page

Disease	Inh	Gene Mutation	Clinical Findings
<b>Familial Mediterranean Fever (FMF)</b>	AR	MEFV (pyrin, also known as marenosttrin)	Recurrent febrile episodes with self-limited but painful episodes of synovitis, peritonitis, pleuritis
<b>Familial Partial Lipodystrophy (FPLD)</b>	AD	LMNA (lamins A and C)	Absence of subcutaneous fat, muscular appearing arms/legs, acanthosis nigricans, diabetes mellitus
<b>Focal Dermal Hypoplasia (Goltz Syndrome)</b>	XLD	POCRN (X chromosome: encodes acyltransferase)	Alopecia, fat herniation, osteopathia striata, mucocutaneous papillomas, and enamel pits
<b>Gardner Syndrome (Familial Polyposis of the Colon)</b>	AD	APC (adenomatosis polyposis coli)	GI polyps, ↑ colon cancer, osteomas (jaw), supernumerary teeth, epidermoid cysts, CHRPE (congenital hypertrophy retinal pigment epithelium)
<b>Gaucher Disease</b>	AR	β-Glucosidase (also known as glucocerebrosidase)	Erlenmeyer flask bone deformity, bone pain, aseptic necrosis, hepatosplenomegaly, ± CNS involvement
<b>Gorlin Syndrome (Nevoid BCC Syndrome) (Basal Cell Nevus Syndrome)</b>	AD	PTCH (patched mutation → SMO activation [Hedgehog pathway] resulting in ↑ Gli)	Palmoplantar pits, jaw cysts, bifid ribs, ovarian fibromas, medulloblastomas, falx calcification
<b>Griselli Syndrome</b>	AR	Rab 27A MyO5A (myosin V)	Pancytopenia, immunodeficiency, silvery gray hair, partial albinism, ↑ infections, neurological impairment
<b>Hailey–Hailey Disease (Familial Benign Chronic Pemphigus)</b>	AD	ATP2C1 (golgi-associated Ca <sup>2+</sup> ATPase, interferes with intracellular calcium signaling)	Flaccid blisters and erosions in intertriginous areas with vegetating plaques
<b>Haim–Munk Syndrome</b>	AR	Cathepsin C	Erythematous PPK, onychogryphosis, periodontitis, early loss of teeth, acroosteolysis
<b>Harlequin Fetus</b>	AR	ABCA12	Restrictive plate-like scales, eclabium, death due to respiratory difficulty and/or sepsis
<b>Hartnup Disease</b>	AR	SLC6A19 (defective intestinal/renal neutral amino acid transport)	Pellagra-like dermatosis with photosensitivity, ataxia, tremors
<b>Hereditary Angioedema</b>	AD	SERPINC1 (gene for C1-INH, serine protease inhibitor)	Episodes of nonpitting swelling (angioedema), ± abdominal pain, diarrhea, paroxysmal colicky pain
<b>Hereditary Congenital Lymphedema (Nonne-Milroy)</b>	AD	VEGFR3 (FLT4)	Congenital lymphedema, chylous ascites, bilateral pleural effusions
<b>Hereditary Hemorrhagic Telangiectasia (Osler-Weber- Rendu)</b>	AD	ENG (endoglin) ACVRL1 (ALK1)	Pulmonary and hepatic AVMs, recurrent epistaxis, visceral hemorrhages (especially GI), telangiectasias
<b>Hermansky–Pudlak Syndrome (HPS)</b>	AR	HPS (lysosomal transport protein)	Oculocutaneous albinism, no dense bodies in platelets, ↑ bleeding, granulomatous colitis, pulmonary fibrosis
<b>Hidrotic Ectodermal Dysplasia (Clouston Syndrome)</b>	AD	GJB6 (connexin 30: gap junction protein)	PPK, nail dystrophy, sparse hair, patchy alopecia, normal teeth, normal sweating, tufting of the terminal phalanges
<b>Holocarboxylase Synthetase Deficiency</b>		HLCS (holocarboxylase synthetase)	Alopecia, perioral and perianal scaly dermatitis, lethargy, difficulty feeding
<b>Homocystinuria</b>	AR	CBS (cystathione b-synthetase)	Marfanoid habitus, downward displaced lens (ectopia lentis), thromboembolic events, neurologic features

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Disease	Inh	Gene Mutation	Clinical Findings
<b>Howel–Evans Syndrome</b> (Tylosis-Esophageal Carcinoma)	AD	TOC (envoplakin)	Focal PPK over pressure areas (balls of feet > hands), oral leukokeratosis, ↑ esophageal carcinoma
<b>Hunter Syndrome</b>	XLR	Iduronate-2-sulfatase	Ivory-colored papules between scapula, cardiac involvement, joint stiffness, mental retardation
<b>Hurler Syndrome</b>	AR	α-L-iduronidase	No skin findings
<b>Hyper-IgE Syndrome</b> (Job Syndrome)	AD (mainly)	STAT3	Recurrent “cold” staph infections, eczema, retained primary teeth, ↑ eosinophils, ↑ IgE
<b>Hypohidrotic Ectodermal Dysplasia (HED)</b> (Anhidrotic Ectodermal Dysplasia) (Christ-Siemens-Touraine)	XR AD AR	EDA (ectodysplasin A) EDAR (EDA receptor) <b>NF-κB</b> critical role	Hypotrichosis, ↓↓ sweating with heat intolerance, periorbital hyperpigmentation, peg-shaped teeth, anodontia, normal nails, saddle facies with large lips
<b>Hypohidrotic ED with Immunodeficiency</b> (HED-ID)	XLR	NEMO (encodes protein nuclear factor <b>NF-κB</b> essential modulator)	Hypohidrotic ED, immune system abnormalities
<b>Ichthyosis Bullosa of Siemens</b>	AD	K2E (keratin 2e)	Hyperkeratotic ridged plaques in flexural areas; tonofilament clumping (upper spinous/granular layers on EM)
<b>Ichthyosis, Lamellar</b> (LI)	AR	TGM1 (transglutaminase 1)	Collodion membrane, plate-like scales, eclabium, ectropion (± incomplete lid closure with subsequent keratitis)
<b>Ichthyosis, X-linked</b> (XLI) (Steroid Sulfatase Deficiency)	XLR	STS (steroid sulfatase)	Corneal opacities, cryptorchidism, testicular cancer, polygonal brown scales (invariably on the neck)
<b>Ichthyosis, Vulgaris</b>	AD	FLG (filaggrin)	Dry skin with scaling (extensor extremities mainly)
<b>Incontinentia Pigmenti</b> (Bloch-Sulzberger Syndrome)	XLD	NEMO (nuclear factor <b>NF-κB</b> essential modulator)	Peg-shaped teeth, eye abnormalities, alopecia, four stages (vesicular, verrucous, hyperpigmented, hypopigmented)
<b>Kindler Syndrome</b>	AR, AD	KIND1 (kindlin-1)	Congenital blistering and photosensitivity, poikiloderma with cutaneous atrophy, PPK
<b>KID Syndrome</b> (Keratitis-Ichthyosis-Deafness Syndrome)	AD mainly sporadic	GJB2 (connexin 26)	Vascularizing keratitis, night blindness, PPK, photophobia, deafness, ichthyosis, symmetric hyperkeratotic ridged plaques (knees, elbows, face)
<b>Leiomyomatosis</b> (Reed Syndrome)	AD	FH (fumarate hydratase)	Cutaneous and uterine leiomyomas, renal cysts, renal cell cancer
<b>LEOPARD Syndrome</b>	AD	PTPN11 (protein tyrosine phosphatase non-receptor type 11)	Lentigines, ECG defects, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retarded growth, deafness
<b>Lesch–Nyhan Syndrome</b>	XLR	HGPRT (hypoxanthine-guanine phosphoribosyltransferase)	Hyperuricemia, self-mutilation, neurologic dysfunction, gout-like arthritis
<b>Lhermitte–Duclos Syndrome</b> (Dysplastic Gangliocytoma of the Cerebellum)	AD (if with Cowden)	PTEN (tumor suppressor gene)	Slowly enlarging mass within cerebellar cortex, cerebellar signs, ↑ intracranial pressure, often associated with Cowden syndrome
<b>Li–Fraumeni Syndrome</b>	AD	P53 (tumor suppressor gene)	↑ Breast CA, ↑ brain tumors, ↑ osteosarcoma, ↑ leukemia (skin cancer not typical feature)
<b>Lipoid Proteinosis</b> (Urbach-Wiethe Disease)	AR	ECM1 (extracellular matrix protein 1)	Waxy yellow papules on face, thick tongue, hoarse cry, hippocampal calcifications, alopecia, row of beaded papules along eyelid margin (string of pearls)

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Disease	Inh	Gene Mutation	Clinical Findings
<b>Lymphedema-Distichiasis Syndrome</b>	AD	FOXC2 (forkhead box protein C2: transcription factor)	Lower-limb lymphedema starting in late childhood, distichiasis (double row of eyelashes)
<b>Maffucci Syndrome</b>	Sporadic	Maybe PTHR1 (parathyroid hormone receptor type 1)	Venous malformations of distal extremities, endochondromas, chondrosarcomas
<b>Mal de Meleda</b>	AR	SLURP1 (encodes protein: secreted Ly-6/uPar related protein)	Transgredient PPK (hands, feet, elbows, knees), hyperhidrosis with malodor and secondary infections, perioral erythema
<b>McCune–Albright Syndrome</b> (Polyostotic Fibrodysplasia)	Sporadic	GNAS1 ( $\alpha$ subunit of stimulatory G protein, Gs, of adenylate cyclase)	Precocious puberty, endocrine hyperfunction, large café-au-lait pigmentation (“coast of Maine”), fibrous dysplasia of bones (may lead to pathological fractures)
<b>MEN 1</b> (Wermer Syndrome)	AD	MEN1 (menin: tumor suppressor gene)	Tumors (parathyroid, pituitary, pancreatic), collagenomas, lipomas, multiple angiofibromas (occurs later than in tuberous sclerosis)
<b>MEN 2a</b> (Sipple syndrome)	AD	RET (renin proto-oncogene: tyrosine kinase receptor)	Macular amyloidosis, hyperparathyroidism, medullary thyroid carcinoma, pheochromocytoma
<b>MEN 2b</b>	AD	RET (renin proto-oncogene: tyrosine kinase receptor)	Mucosal neuromas with thickened lips, marfanoid habitus, medullary thyroid carcinoma, pheochromocytoma, GI problems (i.e., diverticulosis)
<b>Menkes Disease</b> (Menkes Kinky Hair Disease)	XLR	MNK (also known as ATP7a, copper transporting ATPase)	Doughy skin, sparse short hair, pili torti, seizures, growth failure, hypotonia, mental retardation
<b>MIDAS Syndrome</b>	XLD	HCCS (Holocytochrome c-type synthase)	Microphthalmia, dermal aplasia, sclerocornea, $\pm$ cardiac arrhythmias
<b>Monilethrix</b> (Beaded Hair)	AD	K86, K81 (human hair keratin: hHb6 and hHb1)	Normal hair at birth $\rightarrow$ fragile, brittle short hair first few months later, keratosis pilaris, monilethrix (hair fibers with elliptical nodes alternating with abnormal constrictions)
<b>Muckle–Wells Syndrome</b> (Urticaria-Deafness-Amyloidosis)	AD	CIAS1 (cryopyrin)	Episodic fevers, lancinating limb pain, urticaria-like eruption, progressive deafness, $\pm$ amyloidosis (AA)
<b>Muir–Torre Syndrome</b>	AD	MSH2, MLH1, MSH6 (DNA mismatch repair genes)	Sebaceous adenomas and carcinomas, keratoacanthomas, colon cancer
<b>Nail–Patella Syndrome</b> (Hereditary Osteo-Onychodysplasia) (HOOD)	AD	LMX1B (transcription factor that regulates collagen synthesis)	Triangular lunulae, hypoplastic nails, absent patella, scapular thickening, Lester iris, radial head abnormalities, iliac crest exostoses
<b>Naxos Disease</b>	AR	Plakoglobin (cell adhesion protein)	Woolly hair, diffuse PPK, right ventricular cardiomyopathy and arrhythmia
<b>Neimann–Pick Disease</b>	AR	SMPD1 (sphingomyelinase)	Hepatosplenomegaly, thrombocytopenia, ataxia, dysarthria, dystonia, seizures
<b>Netherton Syndrome</b>	AR	SPINK5 (LEKTI: serine protease)	Ichthyosiform linearis circumflexa, atopic dermatitis, trichorrhexis invaginata
<b>Neurofibromatosis I</b> (Von Recklinghausen Disease)	AD	NF1 (neurofibromin: tumor suppressor gene)	Lisch nodules, neurofibromas, café-au-lait macules, axillary/inguinal freckling, $\pm$ learning disabilities, $\uparrow$ tumors (i.e., optic gliomas, malignant peripheral nerve sheath tumors, CNS tumors, juvenile myelomonocytic leukemia)

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Disease	Inh	Gene Mutation	Clinical Findings
<b>Neurofibromatosis II</b>	AD	NF2 (schwannomin, also known as merlin)	CALMs, noncancerous tumors of nervous system (acoustic neuromas, meningiomas, spinal tumors)
<b>Noonan Syndrome</b>	AD	PTPN11 (protein tyrosine phosphatase SHP-2), KRAS, RAF1, SOS1	Lymphedema, keloids, edema over hands/feet, poor tongue control, low-set ears, hypertelorism, low-set hairline at nape of neck, webbed neck, short stature
<b>Occipital Horn Syndrome</b> [(X-linked Cutis Laxa) formerly known as EDS variant]	XLR	ATP7A (copper transporting ATPase)	Skin and joint laxity, pili torti, vascular tortuosity, occipital horns (bilateral occipital exostoses of the skull)
<b>Pachyonychia Congenita, Type I</b> (Jadassohn-Lewandowsky)	AD	K6, K16 (Type 1)	Focal PPK, benign oral leukokeratosis, nail dystrophy (significant subungual hyperkeratosis)
<b>Pachyonychia Congenita, Type II</b> (Jackson-Lawler)	AD	K6b, K17 (Type 2)	Nail dystrophy, steatocystomas, eruptive vellus hair cysts, natal teeth, pili torti
<b>PAPA Syndrome</b>	AD	CD2BP1 (CD2 binding protein 1)	Pyogenic arthritis, pyoderma gangrenosum, acne
<b>Papillon-Lefèvre Syndrome</b>	AR	CTSC (cathepsin C)	Stocking glove PPK, periodontitis, premature tooth loss, dural calcifications
<b>Peutz-Jeghers Syndrome</b>	AD	STK11 (known as LKB1, serine/threonine kinase 11)	Perioral, intraoral and acral lentigines, GI polyps (mainly hamartomatous, not premalignant)
<b>Phenylketonuria</b>	AR	PAH (phenylalanine hydroxylase)	Pigmentary dilution (blonde, blue eyes), eczematous dermatitis, seizures, mental retardation, mousy odor
<b>PIBIDS</b>	AR	ERCC2/XPD (nucleotide excision repair)	Photosensitivity, ichthyosis, brittle hair, infertility, developmental delay, short stature
<b>Piebaldism</b>	AD	KIT (proto-oncogene) (defect in migration/differentiation of melanoblasts from neural crest)	Poliosis (↓ or absence of melanin in scalp hair or eyelashes) often with white forelock, focal areas of leukoderma
<b>Porphyria Cutanea Tarda</b> (Familial Porphyria Cutanea Tarda)	AD	UROD (uroporphyrinogen decarboxylase)	Cutaneous fragility of sun-exposed sites (bullae, erosions, milia, atrophic scars), temporal/malar hypertrichosis, indurated plaques on chest/back
<b>Porphyria, Congenital Erythropoietic</b> (Gunther)	AR	UROS (uroporphyrinogen III cosynthase)	PCT cutaneous findings (often more severe), hemolysis, erythrodontia, infections, hematologic complications
<b>Porphyria, Hereditary Coproporphyria</b>	AD	CPO (coproporphyrinogen oxidase)	Dark urine, photosensitivity, PCT cutaneous findings, episodic attacks of abdominal pain, ± CNS changes
<b>Porphyria, Variegata</b>	AD	PPO (protoporphyrinogen oxidase)	PCT cutaneous findings, neuropsychiatric symptoms
<b>Porphyria, Acute Intermittent</b>	AD	PBD (porphobilinogen deaminase)	No skin manifestation
<b>Porphyria, Erythropoietic Protoporphyria</b>	AD	Ferrochelatase	Photosensitivity with stinging, wax-like scarring, cholestasis, ± liver damage
<b>Progeria</b> (Hutchinson-Gilford syndrome)		LMNA (nuclear lamins A and C)	Premature aging, prominent scalp veins, beaked nose, scleroderma-like skin, short stature, alopecia, atherosclerosis, premature death
<b>Pseudoxanthoma Elasticum</b>	AR	ABCC6 (ABC cassette transporter MRP6)	Small yellow papules, cutaneous laxity (neck, axilla, groin), angioid streaks, calcification of elastic fibers (claudication, myocardial infarction)

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Disease	Inh	Gene Mutation	Clinical Findings
<b>Refsum Syndrome</b>	AR	PHYH (PAHX) or PEX7 (↓ peroxisomal enzyme: phytanoyl CoA hydroxylase)	Retinitis pigmentosa, deafness, peripheral neuropathy, mild ichthyosis, cerebellar ataxia
<b>Richner-Hanhart Syndrome</b>	AR	TAT (hepatic tyrosine aminotransferase)	Pseudoherpetic keratitis, painful focal PPK
<b>Rombo Syndrome</b>	AD	Unknown	Atrophoderma vermiculatum, BCCs, hypotrichosis
<b>Rothmund–Thomson Syndrome</b> (Poikiloderma Congenitale)	AR	RECQL4 (DNA helicase)	Photosensitivity, absent radii, hypoplastic thumbs, premalignant acral keratoses, cataracts, alopecia, nail dystrophy, ↑ osteosarcoma and SCC
<b>Rubinstein–Taybi Syndrome</b>	Sporadic mainly	CBP (CREB binding protein)	Heart defects, beaked nose, broad thumbs, capillary malformations, multiple pilomatricomas, keloids, short stature, mental retardation
<b>Sjögren–Larsson Syndrome</b>	AR	FALDH (fatty aldehyde dehydrogenase, aka ALDH3A2)	Ichthyosis, persistent pruritus, mental retardation, epilepsy, spastic di- or tetraplegia, glistening white perifoveal dots in ocular fundus
<b>Trichorhinophalangeal Syndrome</b>	Sporadic or AD	TRPS-1	Bullous pear-shaped nose, shortened phalanges, brachydactyly, cone-shaped epiphyses
<b>Tuberous Sclerosis</b>	AD	TSC1 (hamartin gene) TSC2 (tuberin gene)	Facial angiofibromas, ash-leaf macules, seizures, shagreen patch, periungual and gingival fibromas, dental enamel pits, neuropsychiatric defects
<b>Uncombable Syndrome</b> (Pili Trianguli Et Canaliculi)	Sporadic or AD	Unknown	Stiff hair with “spun glass” appearance and difficult to comb, triangular shaped shaft (longitudinal groove)
<b>Vohwinkel, Classic</b> (Mutilating PPK)	AD	GJB2 (connexin 26)	Ichthyosis, deafness, starfish-shaped keratotic plaques, pseudoainhum, honeycomb PPK
<b>Vohwinkel, Variant</b>	AD	Loricrin	Ichthyotic variant, no deafness
<b>Waardenburg Syndrome</b>	AD	PAX3 (transcription factor) MITF, SOX10	Dystopia canthorum, white forelock, heterochromia of the eyes, deafness, synophrys
<b>Werner Syndrome</b> (Adult Progeria)	AR	WRN (also known as RECQL2: DNA helicase)	Sclerodermoid changes, ulcerations over bony prominences, ↑ CA, premature aging (cataracts, diabetes mellitus, atherosclerosis, osteoporosis in 20s)
<b>Wiskott–Aldrich Syndrome</b>	XLR	WASP	Eczema, thrombocytopenia, immune deficiency, ↑ pyogenic infections



## 11.2 BUZZ WORDS

"Buzz" words	Association
<b>Oral Findings</b>	
Premalignant oral leukoplakia	Dyskeratosis congenita
Benign oral leukoplakia	Pachyonychia congenita type 1
Cobblestoning of oral mucosa	Cowden syndrome, Crohn's disease
Anodontia	Hypomelanosis of Ito, incontinentia pigmenti, hypohidrotic ectodermal dysplasia
Pegged teeth	Ectodermal dysplasias (i.e., hypohidrotic ED), incontinentia pigmenti
Natal teeth	Pachyonychia congenita type 2
Retention of primary teeth	Hyper-IgE syndrome
Supernumerary teeth (polydontia)	Gardner syndrome
Red-colored teeth (erythrodontia)	Congenital erythropoietic porphyria
Staining of teeth	TCN (gingival 1/3), MCN (middle 1/3)
Enamel hypoplasia (including enamel pits)	Sjögren–Larsson syndrome, tuberous sclerosis, junctional epidermolysis bullosa
Centrally notched upper incisors	Congenital syphilis
Periodontitis with early tooth loss	Papillon–Lefèvre syndrome, Haim–Munk syndrome
Floating teeth	Letterer–Siwe disease (LCH)
Mucocutaneous papillomas and pits	Focal dermal hypoplasia
Mucosal neuromas (± rubbery lips)	MEN 2b (also known as MEN 3)
Oral fibromas	Tuberous sclerosis, Birt–Hogg–Dubé syndrome
Odontogenic cysts	Gardner syndrome, nevoid basal cell carcinoma syndrome (Gorlin syndrome)
Macroglossia	Beckwith–Wiedemann syndrome
<b>Eye Findings</b>	
Comma-shaped corneal opacities	X-linked ichthyosis
Whorl-like corneal opacities	Fabry disease
Keratoconus (gradual bulging from normal round shape to cone shape)	Down syndrome, atopic dermatitis
Painful keratitis, dendritic corneal ulcers (pseudoherpetic)	Richner–Hanhart syndrome
Photophobia, keratitis, neovascularization, eventual blindness	KID syndrome
Anterior subcapsular cataracts	Atopic dermatitis
Lester iris (hyperpigmentation around pupillary margin of iris)	Nail–patella syndrome
Heterochromia iridis (two different eye colors in same individual)	Waardenburg syndrome
Lisch nodules (pigmented hamartomatous nevi in iris)	Neurofibromatosis
Coloboma (defect in iris)	Goltz syndrome
Ectopia lentis (lens dislocation), downward	Homocystinuria
Ectopia lentis, upward	Marfan syndrome
Anterior uveitis, lacrimal gland enlargement with ↑ lacrimation	Sarcoidosis
Uveitis (anterior or posterior), glaucoma	Behcet's disease

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“Buzz” words	Association
<b>Eye Findings (cont’d)</b>	
Angioid streaks	Pseudoxanthoma elasticum, lead poisoning
Congenital hypertrophy of retinal pigment epithelium (CHRPE)	Gardner syndrome
Retinitis pigmentosa (salt/pepper)	Cockayne syndrome, Refsum disease
Perifoveal glistening white dots in ocular fundus	Sjögren–Larsson syndrome
Retinal phakomas (hamartomas)	Tuberous sclerosis
<b>Nose and Ear Findings</b>	
Broad nasal bridge	Hyper-IgE syndrome
Bullous pear-shaped nose	Trichorhinophalangeal syndrome
Beaked nose	Rubinstein–Taybi syndrome, progeria
Circular depression (posterior rim of helices)	Beckwith–Wiedemann syndrome
Ear lobe crease	Beckwith–Wiedemann syndrome
Crumpled ears	Congenital contractural arachnodactyly
<b>Radiologic Findings</b>	
Calcification of falx cerebri	Gorlin syndrome
Calcification of basal ganglia	Tuberous sclerosis, Gorlin syndrome, Cockayne syndrome
Calcification of dura (at tentorium and choroid attachments)	Papillon–Lefèvre syndrome
Calcification of hippocampus and amygdala	Lipoid proteinosis
Tram-track calcification (due to vascular malformations in cortex)	Sturge–Weber syndrome
Occipital exostoses (horns)	Occipital horn syndrome, Menkes disease
Thickening of calvarium	Hidrotic ectodermal dysplasia (Clouston), tuberous sclerosis
Radiolucent “punched out” osteolytic lesions often on skull	Multiple myeloma
Solitary or multiple “punched out” lesions, ± sclerotic rim (skull, mandible, humerus, femur, rib)	Eosinophilic granuloma (form of Langerhans cell histiocytosis)
Wormian bones (additional intrasutural bones within skull)	Osteogenesis imperfecta, Menkes disease
Dysplasia of sphenoid wing (skull bone)	Neurofibromatosis I
Cranial and external auditory canal hyperostosis	Proteus syndrome
Beaded ribs	Osteogenesis imperfecta
Bifid (bifurcated) ribs	Gorlin syndrome
Supernumerary vertebrae	Incontinentia pigmenti
Osteopoikilosis (numerous sclerotic foci in long bones)	Buschke–Ollendorf syndrome
Osteopathia striata (prominent vertical striations near epiphyses/metaphyses in long bones)	Goltz syndrome
Melorheostosis (thickening of bony cortex like ‘dripping candle wax’)	Linear scleroderma
Erlenmeyer flask deformity of femoral mid-shaft	Gaucher disease
Cone-shaped epiphysis	Trichorhinophalangeal syndrome
Stippled epiphyses or chondrodysplasia punctata (punctate calcifications within epiphyseal cartilage)	CHILD syndrome, Conradi–Hünemann syndrome
Absent radii	Fanconi anemia
Hypoplastic radii, ulnae, and/or thumbs	Rothmund–Thomson syndrome
Radial head subluxation	Nail–patella syndrome

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“Buzz” words	Association
<b>Radiologic Findings (cont’d)</b>	
Broad thumbs	Rubinstein–Taybi syndrome
Hypoplastic thumbs	Rothmund–Thomson syndrome
Short 4th metacarpal	Albright’s hereditary osteodystrophy
Clinodactyly	Cornelia de Lange syndrome, Russell–Silver syndrome
Thickened scapulae	Nail–patella syndrome
Absent patella	Nail–patella syndrome
Sclerotic focal bone lesions	POEMS syndrome
Iliac exostoses (posterior iliac horns)	Nail–patella syndrome
Dysostosis multiplex (characteristic skeletal abnormalities)	Mucopolysaccharidosis (MPS) disorders
Resorption of distal phalanges	Scleroderma, Haim–Munk syndrome
Tufting of terminal phalanges	Hidrotic ectodermal dysplasia (Clouston)
<b>Increased Risk of Cancer</b>	
↑ Lymphoreticular malignancy + ataxia, recurrent infections	Ataxia-telangiectasia
↑ Medulloblastoma and fibrosarcomas + ovarian fibromas	Gorlin syndrome
↑ Leukemia or GI CA + photodistributed rash	Bloom syndrome
↑ Renal, thyroid (medullary), colon CA + fibrofolliculomas	Birt–Hogg–Dubé syndrome
↑ Esophageal CA + focal pressure PPK	Howel–Evans syndrome
↑ Thyroid (follicular), breast, colon CA + trichilemmomas	Cowden syndrome
↑ Chondrosarcoma + endochondromas, venous malformations	Maffucci syndrome
↑ Colon CA + odontogenic cysts	Gardner syndrome
↑ Testicular CA + cryptorchidism	X-linked ichthyosis
↑ Sebaceous CA + sebaceous adenomas	Muir–Torre syndrome
↑ Thyroid (medullary) CA + mucosal neuromas	MEN 2b
↑ Renal cell CA + uterine and cutaneous leiomyomas	Leiomyomatosis
↑ Ovarian, lung, colorectal, pancreatic CA + poikiloderma	Dermatomyositis
↑ Acute myelogenous leukemia + neutrophilic dermatosis	Sweet’s syndrome, pyoderma gangrenosum (atypical bullous form)
↑ GI lymphoma + pruritic vesicles (extensor surfaces)	Dermatitis herpetiformis
↑ Juvenile myelomonocytic leukemia + JXG (juvenile xanthogranuloma)	NF1
↑ Various CA (30% of cases) + destructive arthritis	Multicentric reticulohistiocytosis
↑ Renal cell CA (rare) + shagreen patches	Tuberous sclerosis
↑ SCC + leukoplakia, nail dystrophy, bone marrow failure	Dyskeratosis congenita
↑ Osteosarcoma + hypoplastic thumbs, photosensitivity	Rothmund–Thomson syndrome
Glucagonoma (pancreatic tumor) + erythematous plaques (thighs/groin/perineum)	Necrolytic migratory erythema
<b>Vectors and Disease</b>	
<i>Lutzomyia verrucarum</i> (sandfly)	Oroya fever ( <i>Bartonella bacilliformis</i> )
<i>Lutzomyia</i> spp., <i>Phlebotomus</i> spp. (sandfly)	Leishmaniasis ( <i>Leishmania</i> spp.)
Reduviid bug	Chagas disease ( <i>Trypanosoma cruzi</i> )
<i>Xenopsylla cheopis</i> (rat flea)	Plague ( <i>Yersinia pestis</i> )
	Endemic typhus ( <i>Rickettsia typhi</i> )

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“Buzz” words	Association
<b>Vectors and Disease (cont’d)</b>	
<i>Ctenocephalides felis</i> (cat flea)	Cat-scratch disease ( <i>Bartonella henselae</i> )
<i>Chrysops discalis</i> (deer fly)	Tularemia ( <i>Francisella tularensis</i> )
<i>Chrysops</i> , family Tabanidae (deer or mango fly)	Loaisis ( <i>Loa loa</i> )
<i>Glossina morsitans</i> (tsetse fly)	African trypanosomiasis ( <i>T. gambiense</i> and <i>rhodesiense</i> )
<i>Simulium</i> spp. (black fly)	Onchocerciasis ( <i>Onchocerca volvulus</i> )
<i>Culex</i> , <i>Aedes</i> , <i>Anopheles</i> (mosquitoes)	Filariasis ( <i>Wuchereria bancrofti</i> )
<i>Dermacentor andersoni</i> (Rocky Mountain wood tick)	Tularemia ( <i>Francisella tularensis</i> )
	Rocky Mountain spotted fever ( <i>Rickettsia rickettsii</i> )
<i>Amblyomma americanum</i> (lone star tick)	Tularemia ( <i>Francisella tularensis</i> )
<i>Rhipicephalus sanguineus</i> (brown dog tick)	Mediterranean spotted fever ( <i>Rickettsia conorii</i> )
<i>Ixodes dammini</i> (scapularis), <i>Ixodes pacificus</i>	Lyme disease ( <i>Borrelia burgdorferi</i> )
Trombiculid red mites (larval stage: chigger)	Scrub typhus ( <i>Orientia tsutsugamushi</i> )
<i>Liponyssoides sanguineus</i> (mouse mite)	Rickettsialpox ( <i>Rickettsia akari</i> )
<i>Pediculus humanus</i> (human body louse)	Epidemic fever ( <i>Rickettsia prowazekii</i> )
	Relapsing fever ( <i>Borrelia recurrentis</i> )
	Trench fever ( <i>Bartonella quintana</i> )
<b>Infectious Disease Signs</b>	
Red grains (actinomycetoma)	<i>Actinomadura pelletieri</i>
Yellow to brown grains (actinomycetoma)	<i>Streptomyces somaliensis</i>
Pink or cream grains (actinomycetoma)	<i>Actinomadura madurae</i>
White grains (actinomycetoma)	<i>Nocardia brasiliensis</i> and <i>asteroides</i>
Pectinate hyphae (broken comb)	<i>Microsporium audouinii</i>
Bamboo-like hyphae	<i>Microsporium ferrugineum</i>
“Pig snout” conidia	<i>Microsporium nanum</i>
Bullous tinea pedis	<i>Trichophyton mentagrophytes</i>
Spiral hyphae	<i>Trichophyton mentagrophytes</i>
Teardrop-shaped microconidia (‘birds on a wire’)	<i>Trichophyton rubrum</i>
Septate hyphae with reflexive branching	<i>Trichophyton soudanense</i>
Teardrop, balloon and matchstick forms of conidia	<i>Trichophyton tonsurans</i>
Septate hyphae with favic chandeliers	<i>Trichophyton tonsurans</i>
Partial thiamine and inositol requirement	<i>Trichophyton verrucosum</i>
Khaki-colored colony with club-shaped macroconidia	<i>Epidermophyton floccosum</i>
Round cells attached to one another (“chain of coins,” “brass knuckles”)	Lobomycosis ( <i>Lacazia loboi</i> )
Globe-shaped sclerotic cells (“Medlar bodies”, “copper pennies”)	Chromoblastomycosis (dematiaceous fungi)
Photochromogens (mycobacteria)	<i>M. kansasii</i> , <i>M. marinum</i> , <i>M. simium</i>
Broad-based budding with double contoured thick wall	Blastomycosis ( <i>Blastomyces dermatitidis</i> )
Large round organisms with multiple narrow-based buds radiating outward (mariner’s wheel)	Paracoccidioidomycosis ( <i>Paracoccidioides brasiliensis</i> )
Dichotomous branching at 45–60° angle	Aspergillus
Large ribbon-like hyphae with 90° branching	Mucor
Giant sporangia	Rhinosporidiosis ( <i>Rhinosporidium seeberi</i> )

Continued on the next page



“Buzz” words	Association
<b>Infectious Disease Signs (cont’d)</b>	
Morula formation resembling soccer ball	Protothecosis ( <i>Prototheca</i> )
Winterbottom’s sign	Posterior cervical LAD in African trypanosomiasis
Romana’s sign	Eyelid edema and conjunctivitis in American trypanosomiasis (Chagas disease)
Mazzotti reaction	Severe reaction in onchocerciasis associated with diethyl-carbamazine, (when microfilariae killed)
<b>Surgery</b>	
Least inflammatory nonabsorbable suture	Polypropylene (prolene)
Most inflammatory nonabsorbable suture	Silk
Longest lasting absorbable suture for 180 days	PDS (polydioxanone)
Graft with less contraction	Full-thickness skin graft
Graft with less necrosis due to ↓ vascular requirement	Split-thickness skin graft
Local anesthetic with shortest duration	Procaine
Local anesthetic with longest duration	Bupivacaine (etidocaine next)
Derivation of muscles of mastication	First branchial arch
Derivation of facial expression muscles	Second branchial arch
Muscle needed to pull corners of mouth downward	Depressor anguli oris (DAO)
Muscle needed to dilate nostrils	Levator labii superioris alaeque nasi
Sensory innervation to root of nose, lateral nasal sidewalls	Infratrochlear nerve
Sensory innervation to nasal dorsum and tip	External nasal branch of anterior ethmoidal nerve
Sensory innervation to tympanic membrane	Auriculotemporal nerve
Internal and external carotid artery (ICA/ECA) anastomosis	Dorsal nasal artery (ICA) with angular artery (ECA)
Type of excision best over convex surface	S-plasty
Type of excision for reducing length of scar	M-plasty
Process by which synthetic materials (i.e., polyglycolic acid) absorbed	Hydrolysis
Process by which natural material (cat gut, silk) absorbed	Proteolysis
Antiseptic with flammable property	Isopropyl alcohol
Antiseptic inactivated by blood/sputum, ± contact dermatitis	Povidone-iodine
Antiseptic with neurotoxic effects (teratogenic as well)	Hexachlorophene
Antiseptic with ototoxicity and ocular irritation	Chlorhexidine
Scar strength at 2 weeks, 3 weeks, 6 weeks and 1 year	5%, 15%, 40%, 80%
Temperature needed for melanocyte destruction	−5°C
Temperature to destroy skin cancer	−50°C (vs. −25°C for benign lesion)
Temperature for destruction of keratinocyte	−25°C
Maximum safe dose of lidocaine for tumescent anesthesia	55 mg/kg
<b>Miscellaneous</b>	
B cell lymphoma, leg type	More aggressive with poorer prognosis than B cell lymphomas of head/neck
Nodular amyloidosis	AL
Macular and lichen amyloidosis	Keratin-derived
Scleromyxedema	IgGλ

Continued on the next page

“Buzz” words	Association
<b>Miscellaneous (cont’d)</b>	
Psoriasis	↑ K6/16, ↑ involucrin, ↑ ornithine decarboxylase
Differentiate acquired angioedema vs. hereditary angioedema	Check C4 level
Wolff–Chaikoff effect	Side effect from potassium iodide
Hereditary angioedema	Type I: ↓ C2/C4, ↓ functional C1inh
	Type II: normal C2/C4, ↓ functional C1inh
Proteins to maintain HPV replication in basal layer	E1 and E2 proteins
Treatment for erythema nodosum leprosum	Thalidomide
Most common location for superficial spreading melanoma	Back (men), leg (women)
Autoantibody with CCB-induced LE	Anti-SSA (anti-Ro)
Autoantibody with procainamide-induced LE	Anti-histone
Most common cyst on lateral neck	Branchial cleft cyst
Most common cyst on midline of anterior neck	Thyroglossal duct cyst
Treatment for confluent and reticulated papillomatosis of Gougerot and Carteaud	Minocycline × 6–8 weeks
Drug-induced elastosis perforans serpiginosa (EPS)	Penicillamine

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